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Vol. 36 JANUARY, 1950 No. 1

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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Vol. 36, No. 1, January, 1950. The Journal of Pediatrics is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: The United States, its Possessions and Pan-American Countries, $10.00 a year; Canada and other foreign Countries, $11.00 a year. Entered as Second-class matter June 29, 1932, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in the U. S. A.

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The Journal of Pediatrics

VOL. 36 JANUARY, 1950 No. 1

Original Communications

PSEUDOHYPOPARATHYROIDISM (THE SEABRIGHT BANTAM SYNDROME)

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IDIOPATHIC hypoparathyroidism is a comparatively rare disease.[1, 2] Pseudohypoparathyroidism is even rarer. Albright, Burnett, Smith, and Parson[3] reported three patients with this unusual affliction in 1942. They suggested the appropriate and mellifluous eponym of "Seabright bantam syndrome." Since then no new patients have been reported in detail, although Albright and Reifenstein[4] mention a fourth patient observed at their clinic and refer to three others whose cases had been reported to them by other physicians.

The patients described by these authors exhibited the following features: low serum calcium with elevation of serum inorganic phosphorus concentration; symmetrical obesity with round, full facies; stubby fingers, with the index finger longer than the middle finger in their two adult patients; acalcification of tooth roots; and mental retardation in two of the patients. The crucial abnormality was a failure of the appearance of a phosphate diuresis following the intravenous administration of parathyroid extract, such as Ellsworth and Howard[5] had demonstrated in normal subjects. The suggestion was made that end organ (kidney) failure of response to parathormone was responsible for the chemical abberations in the blood present in this syndrome. It was because of this end organ failure that Albright suggested the name of "Seabright bantam syndrome." The Seabright bantam roosters have female tail feathers. Presumably the feathers do not respond to male sex hormones in this species of bird as they do in other species. Albright,[3] by analogy with animal experiments[6] suggested that in these patients overstimulation of the end organ (kidney) by parathormone might produce the abnormal physiology described.

The patient described in the present communication presented the crucial finding defined by Albright and associates[3] (insensitivity to parathyroid extract) and many of the associated physical abnormalities. We have two purposes in mind in reporting this case study: first, to add a single case to the meager literature concerning this disorder, and second, to advance, with some hesitation, an hypothesis regarding its pathogenesis.

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CASE REPORT

D. J. was first seen at the University of Minnesota Hospitals at the age of 2 years, 4 months because of jaundice. She was born following a full-term pregnancy by an uncomplicated spontaneous delivery. Her birth weight was 3.3 kg. Shortly after birth, feeding difficulties were encountered. The child apparently had frequent colicky abdominal pains and did not gain weight properly. At the age of 2 months, she was taken to another hospital because of respiratory difficulties characterized by choking spells. A diagnosis of "enlarged thymus" was made, and an unknown amount of x-radiation was given. At the age of 3 months she was again hospitalized because of spasmodic laryngitis and tracheitis. At this time she had a great deal of dyspnea and required oxygen therapy, penicillin, and a blood transfusion.

At 4 months of age she was treated at still another hospital because of respiratory difficulties. At this time her weight was 4.3 kg. During this period of hospitalization blood examination revealed a hemoglobin of 13.2 Gm. per 100 ml. The total white blood cell count ranged between 2,900 and 4,800 with a normal differential count. Examination of the blood smear revealed polychromasia, anisocytosis, and macrocytosis. Urinalyses were negative. Blood chemical studies revealed the following: fasting blood sugar was 86 mg. per 100 ml., serum cholesterol was 137 mg. per 100 ml., total serum protein was 6.1 Gm. per 100 ml., of which 4.4 Gm. were albumin, and 1.7 Gm. was globulin. The plasma calcium was 5 mg. per 100 ml. and the phosphorus was 7.5 mg. per 100 ml. Roentgenograms of the chest revealed a sharp deviation of the trachea to the right at the level of the clavicle, but there was no evidence of compression. There also seemed to be a soft tissue mass in the superior mediastinum on the right side. Roentgenograms of the wrists revealed normal bone age, but cupping of the distal ends of the ulna and radius was present. Numerous other studies were performed, including assay of pancreatic tryptic activity. This was thought to be low. Fat was found to constitute 67 per cent of the total dry weight of the stool.

She was treated with calcium salts orally, but no response was noted until vitamin D was given intramuscularly in an initial dose of 50,000 I.U. One month later the alkaline phosphatase of the serum was 18 Bodansky units per 100 ml. Roentgenograms of the chest, when repeated, revealed a questionable expanding lesion of the ribs in the left axilliary line, and callus formation was present. It was the impression of the roentgenologist at this time that there were multiple localized areas of "osteitis" with pathologic fractures. One month after the initial dose of vitamin D, an injection of 450,000 I.U. was given and the serum calcium and phosphorus concentrations two weeks later was 9.6 mg. per 100 ml. and 5.2 mg. per 100 ml., respectively. At the time of discharge her diet consisted of protein milk, vegetables and bananas, and added calcium gluconate. No reasons were advanced to account for the x-ray findings of "osteitis." It was thought, though, that the patient suffered from some form of intestinal insufficiency.

At the age of 9 months she was hospitalized for nearly one year because of marked icterus, hepatomegaly, and abdominal distention. Repeated examinations of duodenal secretions revealed lack of pancreatic ferments. During this period she had repeated bouts of bronchitis, and on one occasion bronchopneumonia. She was given a diet which included protein milk, vegetables, beef and liver, and a supplement of vitamins A, B, and D. The icterus did not recede, and at the age of 2 years 4 months, she was admitted to the University of Minnesota Hospitals for the first time.

Physical examination revealed a small, icteric, white female, who showed evidence of malnutrition and had thin, wasted extremities. Her weight was

8 kg. and her height 69 cm. The abdomen was protuberant with tympanities, but ascites was not noted. The liver was palpable 4 cm. below the xiphoid and 6 cm. below the right costal margin in the midclavicular line. The spleen was palpable 2 cm. below the left costal margin. Her skin was deeply icteric, thickened, and lichenified; wrinkling was noted over the dorsum of the hands and feet. Her hair was very coarse and sparse. Numerous excoriations of the skin were also present.

Initial laboratory studies revealed the following: hemoglobin 9.7 Gm. per 100 ml., red count 2.8 million, white count 11,900, with a differential count of 34 per cent neutrophiles, 65 per cent lymphocytes, and one per cent monocytes. Urine sediment initially contained numerous white cells, but numerous other urine examinations and blood urea nitrogen determinations were normal. Blood chemical studies revealed the following: carbon-dioxide combining power 50 volumes per cent, calcium 6.7 mg. per 100 ml., and phosphorus 4.3 mg. per 100 ml. Carotene level in the blood was too low to measure, and vitamin A was 10 Blue units per 100 ml. Roentgenograms of the chest and skull were normal. Roentgenograms of the abdomen revealed multiple calculi within the gall bladder. Liver function studies and fat absorption determination were both abnormal. Serum bilirubin was 2.9 mg. per 100 ml. free, and 5.7 mg. total. The urine urobilinogen was 0.1 Ehrlich units, the cephalin-flocculation test was normal as was a thymol turbidity test. Serum alkaline phosphatase was 5.1 Bodansky units per 100 ml. Duodenal fluid was normal in respect to tryptic activity. By roentgen examination, the skull appeared normally and symmetrically developed and the anterior fontanel was open. The suture lines were normal. There was neither evidence of intracranial calcification nor any suggestion of hyperostosis of the bones of the base. Two carpal ossification centers were present at the wrist and a very small nidus of ossification in the epiphysis for the distal end of the radius. There was no definite abnormality of the mineralization or trabecular pattern of the bones of the hand, wrist, or forearm at that time.

Biliary exploration was performed and the gall bladder was removed. A biopsy of the liver revealed capillary thrombi and some central degeneration of the liver cells. Following surgery, the jaundice began to recede, and the patient was discharged.

Her progress was followed in the pediatric outpatient department for the next ten months. The icterus receded completely within two months, but the child continued to have extreme pruritus which failed to respond to medication. Three months after discharge the patient was noted to have increased tonicity of the extremities and to hold her hands in a peculiar fashion. Since she had been taking only one glass of milk daily, and was suspected of having tetany, her physician prescribed calcium medication by mouth. With this therapy relief from symptoms was noted.

She was admitted to the hospital for the second time at the age of 3 years, 9 months—seventeen months after her initial admission. At that time she had gained 4 kg. in weight and 12 cm. in height. The liver was palpable 3 cm. below the right costal margin and numerous excoriations of the skin were still present. Liver function studies were similar to those obtained during the previous admission except that the serum bilirubin was now normal and the alkaline phosphatase had risen to 35 Bodansky units per 100 ml. The blood chemical studies at that time revealed that the calcium was 8.2 mg. per 100 ml. and the phosphorus was 6.9 mg. per 100 ml. Roentgenograms of the hands and feet revealed some disturbance in the medullary trabeculation. The trabecular pattern of the bones of the hands was coarse and irregular with an apparent deficiency in the finer trabeculae, producing an appearance almost suggestive of cystlike spaces in the diaphyseal portions of the bone. The carpals and metacarpals appeared rather thick, and the first metacarpals bilaterally showed an expansion of the

distal portion of the shaft with the central portion slightly constricted (Fig. 2, *A*). The bones of the forearms appeared fairly well mineralized, although here, too, there was slight suggestion of coarsening of the trabecular pattern. An intravenous pyelogram was normal. At this time biopsies of the liver and mesenteric lymph nodes were obtained. These were found to be normal. Psychometric evaluation revealed a somewhat retarded child. She was again discharged on a general diet with a supplement of 1,000 I.U. of vitamin D per day.

At the age of 4 years, 4 months, she was admitted to the hospital for the third time. (Figs. 1*A* and 1*B*.) During the interim she had had one episode of

Fig. 1*A*.—Patient at 4 years, 6 months. Note the unusual roundness of the face and the sparse hair. Because of severe pruritus, the patient scratched herself incessantly and produced many excoriations, some of which are visible on her face and shoulders.

Fig. 1*B*.—Hands and feet of patient at 4 years, 6 months. Note stubby fingers and toes and thick pad of skin over dorsum of hands and feet.

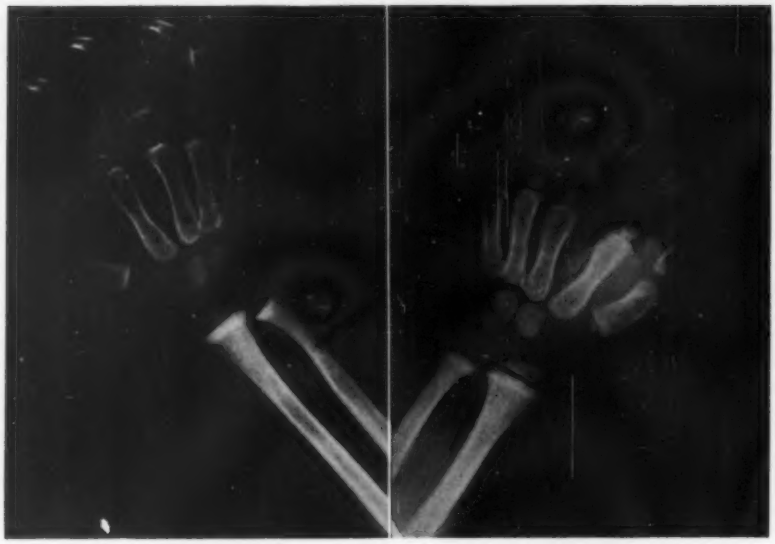
respiratory infection followed by hematuria. This responded to conservative measures. Her weight was 12.4 kg.; her height was 82.5 cm. Physical examination revealed abdominal distention, and a liver enlarged to 3 cm. below the right costal margin. The concentration of calcium in the blood was 10.2 mg. per 100 ml. and that of phosphorus was 6.2 mg. per 100 ml. Fat absorption was found to be 65 per cent. In an attempt to explain the persistent pruritus, serum bile-salt determinations were performed. The concentrations of these were normal. The urine was always normal.

At this time a diagnosis of hypothryoidism was entertained in spite of the fact that radioactive iodine uptake was normal. Desiccated thyroid was given in daily doses of 190 mg. This was continued for a period of three months. During the period of treatment, some improvement in the skin was noted and it appeared more moist. The child was also more alert and active.

Three months later, cramping of the muscles of the hands, feet, and legs was noted. This recurred intermittently and became severe enough to require hospital admission. The patient was then 4 years, 7 months old. Physical examination at this time revealed that the liver was 5 cm. below the right costal margin. The nails revealed transverse ridges in their midportions. Her skin seemed softer and her hair was more plentiful. A positive Chvostek sign was elicited. Blood chemical studies revealed that the serum calcium was 5.5 mg. per 100 ml. and the phosphorus was 7.0 mg. per 100 ml. while the serum protein was 7.1 Gm. per 100 ml. Urinary calcium excretion was 13.1 mg. in a twenty-four-hour period, and urinary phosphorus excretion was 288 mg. per twenty-four hours. She was treated with vitamin D and intravenous and oral calcium salts and was placed on a low fat diet. Intravenous calcium salts immediately relieved the acute symptoms of tetany, but therapy with oral calcium salts neither decreased the frequency or severity of the attacks, nor did it alter the abnormal calcium and phosphorus concentrations in the blood. Because of her failure to respond to this therapy, studies were carried out to determine renal response to parathyroid extract as suggested by Ellsworth and Howard[5] and Albright.[3] (See Table I for details.) The studies revealed no increase in urinary phosphate excretion following intravenous administration of parathyroid extract.* The potency of the parathyroid extract was demonstrated in a normal child.

Roentgenograms of the wrists and spine were obtained. The coarsened trabecular pattern of the bones of the hands was still present. A zone of hypercalcification in the distal radial metaphysis likewise was noted. The development of the epiphyses for the metacarpals and phalanges was within normal limits; the development of the proximal phalanges of the thumbs, however, was markedly delayed, there being only very minimal evidence of ossification in this epiphysis. There was a peculiar notching of the margins of the metacarpals, particularly the first, second, and third in the distal metaphyseal regions, producing an unusual irregular appearance of these bones in this region. (See Fig. 2, *B*.) The coarsening of trabeculation was also apparent in films of the right lower extremity, particularly in the tarsal bones and in the tibia. There was also a band of somewhat increased density in the metaphyses of the tibiae and, to a lesser extent, in the lower metaphyses of the femura. The crowns of the unerupted teeth were mineralized with the root portion of the tooth appearing radiolucent. No roentgen abnormality of the teeth was apparent. Coarsened trabeculae were prominent throughout the bones of the spine, the pelvis, and the upper femora. (See Fig. 2 *C*, *D*.) The trabeculae were somewhat atypically arranged, and the presence of rather dense coarse trabeculae, somewhat more sparsely scattered than usually seen, gave a rough spongy appearance to the bones. Slit-lamp examination of the eyes revealed punctate white, sharply

*Parathyroid extract, 100 U.S.P. units per milliliter. (Eli Lilly and Co.)

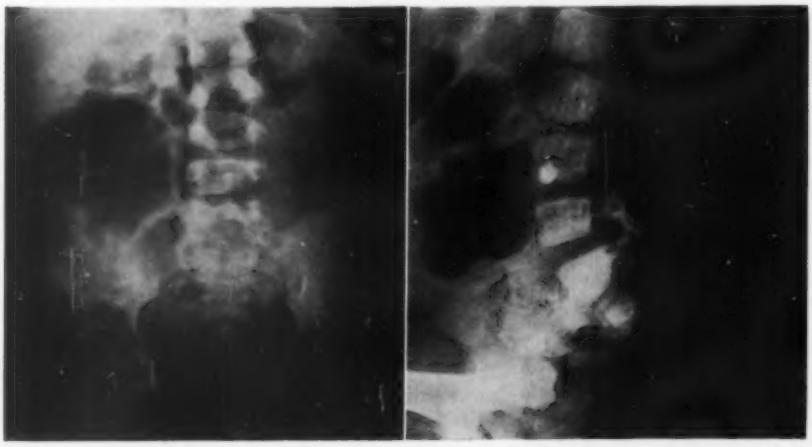


A. *B.*

Figs. 2*A* and 2*B*.—Note irregular trabeculation of carpals, metacarpals, and phalanges and foreshortening of the metacarpals. Also note the increase in density of the radial metaphysis in ten months.

A, Hand and wrist at 3 years, 9 months.

B, Hand and wrist at 4 years, 7 months.



C. *D.*

Figs. 2*C* and 2*D*.—Note the irregularity of calcification of the bones with alternation of dense and rarefied areas.

C, Pelvis at 4 years, 6 months.

D, Lumbar spine at 4 years, 6 months.

TABLE I. VALUES FOR CALCIUM, PHOSPHORUS, AND PHOSPHATASE CONCENTRATION IN THE BLOOD AND CALCIUM AND PHOSPHORUS IN THE URINE, INCLUDING RESPONSE TO INTRAVENOUS ADMINISTRATION OF PARATHORMONE

	BLOOD			URINE			
DATE	CALCIUM (MG./100 ML.)	PHOSPHORUS (MG./100 ML.)	PHOSPHATASE* (PER 100 ML.)	CALCIUM (MG.)	PHOSPHORUS (MG.)	TIME OF COLLECTION (HOURS)	MEDICATION
1/ 1/45	5	7.5					Parenteral vitamin D
1/25/45	9.6	5.2					←
12/ 5/46			5.1 B.U.				
12/23/46			26.1 B.U.				
1/13/47	6.7	4.2					
5/27/47	8.2	6.9	71.5 K.A.				
6/ 1/48	11	6.8					
11/10/48	10.2	6.2					
2/23/49				13.1	288	24	
2/24/49	5.6	7.0	77 K.A.		73	4	Parathormone (100 units)
2/24/49		6.3			65	4	←
3/ 2/49	6.0	4.0			23.5	4	Parathormone (200 units)
3/ 2/49	7.6	4.7			22.4	4	←
3/15/49	6.9	4.4					Large doses vitamin D (Perorum)
3/28/49	10.8	3.3	53 K.A.				←
5/18/49				15.7	45	24	
5/20/49	9.3	5.4		0	44	4	Parathormone (200 units)
5/20/49	10.2	5.3		4.4	24	4	←
5/25/49	9.3	5.6		0.9	109	4	Parathormone (200 units)
5/25/49	10.2	7.4		0.6	50	4	←
			Normal Control				
	9.4	4.1			30	4	Parathormone (100 units)
	9.1	4.4			51	4	←

*B.U., Bodansky units.
K.A., King-Armstrong Units.

demarcated opacities in the deeper layers of the lens cortex both anteriorly and posteriorly.

The child was then placed on a diet normal in fat but low in phosphorus, supplemented with oral synthetic vitamin D in doses of 150,000 I.U. a day, and calcium gluconate 9 Gm. a day. The vitamin D was increased to 200,000 I.U. daily ten days later. On this regimen the tetany was completely relieved. Prior to institution of vitamin D therapy, the serum calcium was 5.9 mg. per 100 ml., and the phosphorus 6.3 mg. per 100 ml. One week later the calcium had risen to 6.9 mg. and phosphorus had fallen to 4.4 mg. Twenty days after therapy was begun the serum calcium was 10.8 mg. and the phosphorus was 3.3 mg. per 100 ml. Alkaline phosphatase decreased from 70 K.A. units prior to therapy to 53.4 K.A. units twenty days later. Vitamin D intake was decreased to 25,000 I.U. daily, three weeks after studies revealed normal amounts of calcium in the urine.

During the period of vitamin D therapy, the patient had repeated epistaxis and numerous echymoses were noted on her extremities. The prothrombin time was greater than 5 minutes while a control was 13.1 seconds. Following treatment with vitamin K and blood transfusions, the bleeding was controlled and the prothrombin time returned to normal. At the time of discharge, serum calcium was 11 mg. and phosphorus was 4.5 mg. per 100 ml. Urinary calcium excretion was 124 mg. per twenty-four hours. The child was kept on a normal fat, low phosphorus diet and given 6 Gm. of calcium gluconate and 25,000 I.U. of vitamin D daily.

One month later the patient was readmitted to the hospital to repeat the studies of serum calcium and phosphorus metabolism. At that time the blood calcium was 9.8 mg. and the phosphorus was 6.1 mg. per 100 ml. The phosphatase was 58 K.A. units per 100 ml. Urinary phosphorus excretion studies following injection of parathyroid extract confirmed the original observation. (See Table I.) There was no phosphate diureses after 200 units of parathyroid extract were administered intravenously. She was discharged while receiving 10 Gm. calcium gluconate and 35,000 I.U. of vitamin D daily.

DISCUSSION

We would like to emphasize the following features of this patient's complicated history: (1) The probable existence of lifelong steatorrhea, (2) the occurence of laryngeal stridor at 3 months of age, (3) the occurrence of hypocalcemia and hyperphosphatemia at 4 months of age, (4) the return of the concentration of calcium and phosphorus in the blood to normal levels following parenteral administration of large doses of vitamin D, (5) poor calcium intake in the period immediately preceding the appearance of tetany at 4 years, 7 months of age, (6) elevated serum alkaline phosphatase, even during a period when there was neither clinical nor laboratory evidence of liver disease, (7) lack of evidence of osteomalacia in roentgenograms of the bones, but with definite interference with normal trabecular structure, this being characterized by intermingling of abnormally dense with abnormally rarified areas, (8) the presence of unusually dense metaphyseal bone, and finally, (9) failure of appearance of phosphate diuresis following intravenous administration of parathyroid extract.

It seems plausible that the sequence of events in the pathogenesis of the patient's disease was as follows: her primary disease was steatorrhea. This evidently had been present since very early in life, though no cause for it could be determined. This steatorrhea caused malabsorption of the fat-soluble vitamins. We have direct evidence that absorption of vitamin A was low, inasmuch as measurement of it in the blood gave very low values. That the absorption of vitamin K was poor was evidenced by the development of hypoprothrombinemia. We can reason that the absorption of vitamin D was poor both by analogy with other patients in whom this has been demonstrated[7] and by the fact that she responded to parenteral medication with this vitamin.

Secondary to the malabsorption of vitamin D, the patient failed to absorb calcium from her intestines. This in turn caused hypocalcemia and tetany. Whether the episode of laryngeal stridor at 3 months of age represented infectious laryngitis or hypocalcemic laryngitis we have no way of knowing.

At 4 months of age the patient had values of calcium and phosphorus in her blood consistent with hypoparathyroidism, but whether she, at that time,

already had the Seabright bantam syndrome, or merely the hypocalcemia that is seen in association with steatorrhea[8] we cannot tell. In favor of the latter is the fact that x-ray examination of the wrists showed changed compatible with rickets, and rickets does not usually occur secondary to hypoparathyroidism.[4] In any case, we have laboratory and clinical evidence that parenterally administered vitamin D relieved her symptoms.

During the next four years the steatorrhea continued, and from the history given by the patient's mother, the intake of milk, and hence calcium, was poor. It also appears reasonable to us that the presence of poor absorption of vitamin D, concomitant malabsorption of calcium from a diet low in that element, and secondary hypocalcemia caused prolonged parathyroid stimulation. Furthermore, all of the changes in skin, hair, nails, and eyes (lenticular opacities) have previously been reported in patients with hypocalcemia from other causes.[9, 10] The abnormal metacarpals were probably secondary to alterations in calcium metabolism and not specifically due to hypoparathyroidism.[4]

If one accepts the fact that this patient initially had aberrations in calcium and phosphorus metabolism secondary to steatorrhea, then the initial bone disease that she had was osteomalacia,[8] and the elevated serum alkaline phosphatase which ordinarily is not noted in hypoparathyroidism[4] would be compatible with this. This might explain why the bones showed rarifaction as well as increased densities by x-ray.

Parathormone exerts its effect upon the phosphorus concentration of the blood by its inhibition of renal tubular reabsorption of phosphorus from the glomerular filtrate.[4] Albright[4] has proposed that the defect in hypoparathyroidism causes: first, an elevation in serum phosphorus concentration, and second, a fall in serum calcium concentration. If this is true, then the serum, at times, must be supersaturated with respect to calcium phosphate. Unsaturation occurs with the compensatory lowering of serum calcium, but while the serum is supersaturated, calcification may occur in the soft tissues of the body. This has been noted in the basal ganglia,[11, 12] around joints[4] and in the lens of the eye.[13] Accepting this sequence of events as correct, one might be permitted a conjecture concerning the cause of the osseous abnormalities demonstrated by x-ray examination of our patient. The dense metaphyseal lines seen at both wrists represent excessive calcification. Similarly, throughout the long bones and vertebral bodies there was dense ossification as well as disordered trabeculae. This, too, would be compatible with hypoparathyroidism.

In summary then, one might account for all of this patient's abnormalities in terms of steatorrhea. The failure of renal response to parathyroid extract might be likened to an "escape" phenomenon in which, because of continued overstimulation, the kidneys had become refractory to parathormone. This explanation receives support from two sources. First, patients[14] and experimental animals[6] frequently become refractory to prolonged administration of parathyroid extract.[14] Second, animals maintained on low-calcium diets very rapidly become resistant to parathyroid extract.[15]

With this patient's clinical history in mind, and considering the two pertinent experimental reports, we suggest that some cases of the Seabright bantam syndrome or conditions simulating it may have as their cause, chronic overstimulation of the renal tubules by the parathyroid gland, with eventual failure of response of these end organs.

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GLYCOGEN DISEASE RESEMBLING MONGOLISM, CRETINISM, AND AMYTONIA CONGENITA

Case Report and Review of Literature

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New Haven, Conn.

THE difficulties encountered in the early diagnosis of mongolism and cretinism are well known to pediatric clinicians. Textbooks for years have arranged in tabular form the similarities and differences of these two syndromes. When a young infant presents several features of each of these conditions and then in addition shows the typical signs, neurological examination, and course characteristic of classical amyotonia congenita of the Oppenheim type, the plot appreciably thickens. Furthermore, when the patient goes on to an exitus entirely in keeping with this last-named disease and then at post-mortem examination is found to have advanced and widespread glycogen storage disease, confidence in one's diagnostic acumen is at least shaken. Because we have recently been through such a confusing series of events and have learned much from the extensive post-mortem findings, we are reporting our experience in detail.

D. B. was a full-term, white, female infant who was born at the New Haven Hospital on March 22, 1948. From the day of her birth until her death at 6 months of age she was seen as a private patient of one of us (D. H. C.) at intervals of no more than a month and frequently shorter. The family history was not remarkable. Both parents are of Anglo-Saxon stock and both are in their early twenties. There was no history in either family of recognized metabolic disease. The mother has one brother who has been mentally defective since birth, presumably because of birth injury. He does not have any enlargement of heart, liver, or spleen. The mother had never been pregnant before. Her health during the pregnancy was excellent. She was not aware of suffering from any infection other than an occasional head cold. She first noted fetal movements at approximately the fourth month and thereafter felt that she was carrying a very active fetus, though she obviously had no basis for comparison.

The infant was delivered spontaneously after seven hours and forty-five minutes of uneventful labor, ten days after the expected date of confinement. She cried at once and her color quickly became pink and remained so. The birth weight was 3,775 grams. Measurements were: head, 34½ cm.; chest, 33½ cm.; length, 51½ cm.; fontanel, 3 by 3 cm. Examination at several hours of age showed the color and cry to be good, but activity was sluggish. The Moro reflex was slow. The muscle tone was poor.

The facies even at birth were remarkable in that a very large tongue protruded and prevented the mouth from closing. The bridge of the nose was sunken. There was no epicanthus. The heart and lungs were not remarkable to physical examination and the extremities were normal in appearance. Liver and spleen were not enlarged to palpation.

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The course in the hospital was not remarkable. Although the weight fell to 3,535 grams on the third day of life, the patient was discharged home on the sixth day weighing 3,740 grams just below birth weight. She sucked well and appeared to thrive on the hospital's stock formula satisfactorily and, although she regurgitated some about every other day, her weight gain was good. Her length ran on the 90th percentile or above and her weight remained at or above the 50th percentile up to the fifth month of life. She took her formula well up to the age of 3 months. Thereafter increasing difficulty was experienced, until what appeared to be a true dysphagia developed in the last three months of life.

At 4 weeks of age the baby followed bright objects with her eyes. At 6 weeks she first smiled. At this time she slept well for eight hours at night, but received six feedings during the day. At 7 weeks when the child was seen in the office, the macroglossia remained marked, and in addition a small umbilical hernia was noted. The nose configuration was as described above. Furthermore the baby appeared to be very sluggish. The upper lids drooped moderately and the extremities moved little. The legs especially lay motionless much of the time, with the hips externally rotated and the knees moderately flexed in a typical "frog leg" position. Tendon reflexes were not obtainable in the legs. The biceps and triceps jerks were sluggish but present in the arms. At 8 weeks cereals were attempted but without success. At 10 weeks fruits were similarly tried but failed. Some time later cereal was fed in the milk mixture through an enlarged nipple hole but solid foods were never successfully fed from a spoon until a few days before death.

At 2½ months of age the infant batted at objects in her crib and for the first time was reported to have laughed aloud. At about this time, however, feeding her became more of a problem, so that by 11 weeks of age her total daily intake of formula was down from 25 ounces to 15 ounces. This was taken in six feedings at about three-hour intervals between 8 A.M. and 11 P.M. The feedings would thus average only 2½ ounces and would take about twenty-five minutes. At this time, too, constipation became a real problem, presumably because of the diminished intake. The baby seemed happy, however, and rarely cried. The mother reported that the child reached for and held in both hands objects dangled above her when she was supine. Examination at 11 weeks found the child to be very drowsy as before. The umbilical hernia had almost disappeared, the tongue remained very large and protruded, and the hands and feet felt cool. The nose configuration remained unchanged. The heart sounds were normal in quality and rapid. There were no murmurs. The lungs were clear.

At 3¼ months (14 weeks) the infant was still unable to take solid food. She appeared to like applesauce, for instance, but vomited or regurgitated it. Constipation remained a great problem. Examination showed no change in the facies, tongue, heart, and lungs. At this time, however, the hands and feet were warm and pink. The pulse was normal or slightly increased. It was noted that the liver was down two fingerbreadths in the midclavicular line. The spleen was not palpable. When the infant was placed in the prone position, she was unable to lift her head off the table, even though her face was pressed against the surface and breathing was made difficult. She had never been able to do this at any time.

At this point (3½ months) x-ray films of the hands and wrists were taken to determine bone age in connection with possible cretinism (facies, tongue, macroglossia, umbilical hernia, cool extremities, rarely cried, gained on small intake, etc.), and films were also made of the heart to determine size and configuration in connection with possible cretinism or mongolism (facies, tongue,

macroglossia, marked generalized hypotonia). Examination of the wrists showed two ossification centers in the carpal bones, well within normal limits for age. Films of the heart, however, revealed that it was markedly enlarged in its transverse diameter (Fig. 2A). The apex was observed to point up, indicating right ventricular enlargement. The lateral films were consistent with this, in that there was some bulging anteriorly. The left ventricle was also noted to be somewhat enlarged in the lateral and oblique views. The lung fields were clear bilaterally. The final diagnosis offered by the roentgenologist was "Cardiac enlargement (left and right ventricular), congenital heart disease."

At 16 weeks the baby was taking almost no solid food. She was still unable to lift her head from the examining table when in the prone position. There continued to be little movement of the legs. Because of this discrepancy between her motor development and her general responsiveness and interest in her environment, the child was referred to the Clinic of Child Development for examination. At the time we were genuinely concerned over the possibility of some mental retardation as well.

We are indebted to Dr. Robert C. Wheeler of that clinic for his careful examination of the baby and we quote freely from the report of his findings:

"D. B. was examined on July 29, 1948, at 18 weeks of age. At first glance she presented the gross picture of a severely retarded child. She lay inactive, her arms and legs passively outstretched at her sides, and her head predominately in the half side position. Her face had a blank expression, with narrow palpebral fissures, and a large relaxed tongue protruded from her mouth. On examination, however, functional exploitative behavior proved to be well developed. She became animated and excited when test objects were presentd. She had prehensory approach and grasp, regard and mouthing for an object in hand, incipient bimanual manipulation, intent regard for a minute object (pellet), hand play, laughter, squealing, patting of her bottle, and pulling her dress over her face. All of this behavior is typical of normal 18- to 20-week development. Her real deficiency was in the gross motor field, where she was near the 4-week level or even lower. When pulled to the sitting position, there was complete head lag, and the lack of normal muscle tone was further demonstrated by ventral suspension where she hung drooping passively. When placed in prone she lay flat and motionless, and there was no effort to raise her head. Her grasp was feeble, and objects were retained but a few seconds. No evidence was found of muscle paralysis or atrophy, but on palpation the muscles were soft and hypotonic. The tendon reflexes were absent.

"With this evidence of normal development in all fields except the motor, we were able to rule out the question of generalized development retardation, and with it diagnoses such as primary amentia, cretinism and mongolism which had been previously considered.

"She presented then the problem of an infant of normal mentality and normal development with the exception of a gross motor disability characterized by a generalized muscular weakness, hypotonicity, and absent deep tendon reflexes. On this basis, suspecting disease of the spinal cord involving lower motor neurons, a diagnosis of amyotonia congenita of the Oppenheim type was postulated."

At 4½ months the infant was reported by the mother as being definitely more observing. She was said to get from one part of her crib to another and had been seen to roll from her side to her abdomen. Examination at this time, however, was characterized by almost no movement of arms or legs when the child was supine. Furthermore the only tendon reflex obtainable was a feeble right knee jerk. The lungs were clear and the heart sounds normal, but the

pulse was 120 and the respirations 60. The patient was free of evident infection or fever at the time. Her color was poor, and could be best described as a gray pallor. There was no true cyanosis, even of the nail beds. The liver enlargement noted previously persisted. The picture was consistent with chronic congestive heart failure.

Since the question of amyotonia congenita had been raised, the baby was referred for consultation to a competent pediatric neurologist, Dr. Herman Yannet. He found marked weakness of the neck, back, arm, and leg muscles and was unable to elicit any of the deep tendon reflexes. He noted some shortening of the hamstrings, felt the baby's mentality was adequate but that she had a marked motor deficit. He concluded that "the picture is compatible with a mild degree of amyotonia congenita." He pointed out that two features of the infant's examination were not satisfactorily explained by this diagnosis: the marked macroglossia and the congenital heart disease. He felt there was no evidence of hypothyroidism.

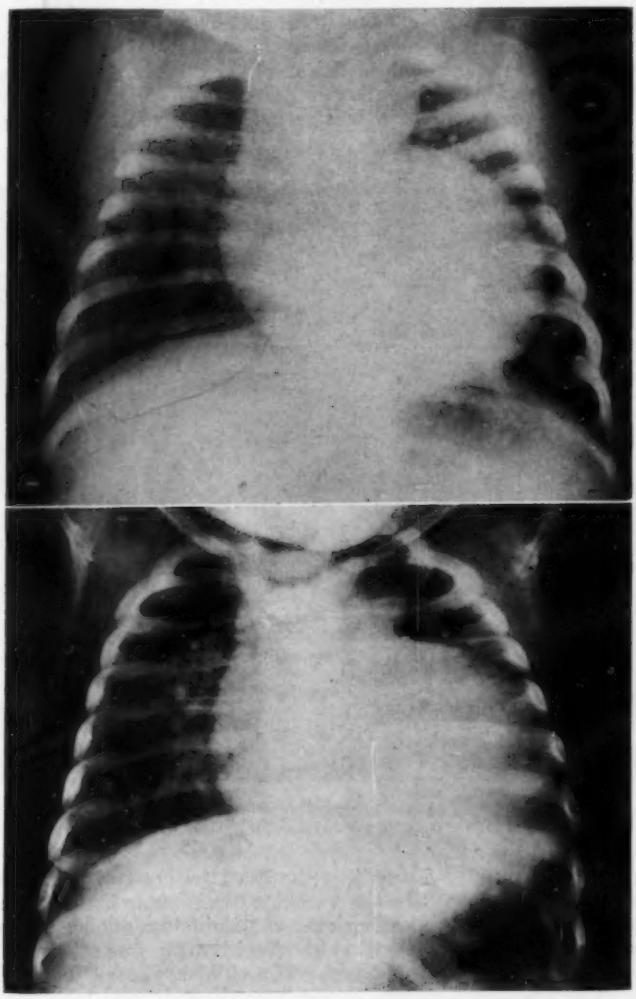
Fig. 1.—Patient at age 5½ months with parents. Note facies, protruding tongue, and inability to support head or sit alone.

At 5½ months of age the baby experienced much more difficulty with feeding. As little as one-half ounce at a time would be taken and the twenty-four-hour intake was only 12 to 14 ounces of formula. Swallowing seemed to hurt her. She became much more irritable, cried most of the night and much of the day, and slept poorly. This state of affairs existed for the last three weeks of life. The mother felt that the baby's legs were more active, however.

Noteworthy features of this last routine physical examination before the terminal illness include a grayish pallor, the absence of cardiac murmurs, and a liver edge that was felt two fingerbreadths below the costal margin. The macroglossia and generalized hypotonia of the muscles persisted. (Fig. 1.)

On Sept. 10, 1948, ten days before her death, the infant's father developed diarrhea and a fever of 39.7° C. The baby had three loose stools five days before death but thereafter had no diarrhea. After three days of unusual irritability, the child was noted to be warm and breathing more rapidly than before. She was seen by one of us and was immediately hospitalized on Sept. 20, 1948. Temperature was 40° C., pulse 180, respirations 60. The baby was obviously acutely ill. The breathing was chiefly abdominal and there was dilation of the alae nasi. Other noteworthy findings included moderate pharyngeal

A.



B.

Fig. 2.—*A*, Teleoroentgenogram of heart taken at age of 3½ months. *B*, Teleoroentgenogram of heart taken at age of 6 months, the day before death.

injection, some retraction of the lower ribs, cardiac dullness out to the mid-axillary line, a loud rough systolic murmur best heard at the point of maximal impulse which was well outside the left mid-clavicular line, diminished breath sounds and crepitant râles at the left base posteriorly, a liver edge felt three fingerbreadths below the costal margin, a spleen that was not palpable, and extremities that were rarely moved voluntarily, showed flabby, hypotonic muscles, and were completely lacking in tendon reflexes.

Laboratory data included a red cell count of 5 million per cubic millimeter hemoglobin 12.5 Gm., white cell count 21,000 per cubic millimeter, with band forms 6 per cent, polymorphonuclears 54 per cent, lymphocytes 36 per cent, and monocytes 4 per cent. Cultures from the nose and throat yielded only the usual flora, and cultures of the blood and spinal fluid were sterile. The spinal fluid showed no other abnormalities. An x-ray film of the chest showed a markedly and symmetrically enlarged heart which filled almost the entire left crest. There was pneumonic infiltration in the right middle and right lower lobes. (Fig. 2*B*.)

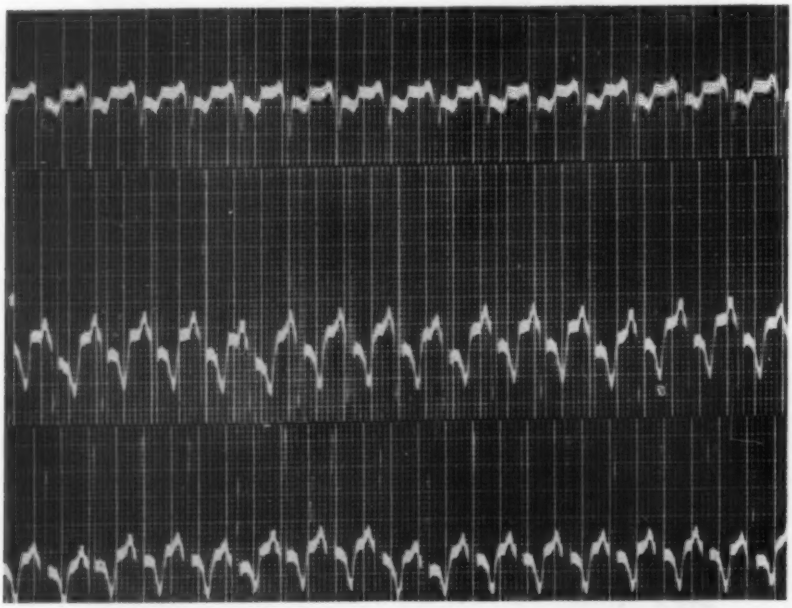


Fig. 3.—Electrocardiogram taken on day of death at 6 months of age. From the top to bottom are shown conventional Leads I, II, and III.

The child went rapidly downhill. She lived twenty-two hours in the hospital. During this time the lung signs changed to tubular breathing at the left base posteriorly with some appearing over the right lower lobe. Breathing remained largely abdominal and very rapid. Tachycardia was constant, the pulse feeble, and the extremities became cool. The child appeared to go into shock. Before Digifolin was administered, an electrocardiogram was taken on Sept. 21, 1948, the day of death. This is reproduced in Fig. 3. We are indebted to Dr. Ruth Whittemore for the following interpretation: "Rate: 167. P-R interval:

0.08. Rhythm: sinus tachycardia. QRS: duration 0.06. Amplitude: abnormally large deflections, 40 or more millivolts in each lead, in some instances completely leaving the record. Contour: deep Q_2 and Q_3. RS-T: Abnormally depressed in all three standard leads. T waves: Biphasic T_1 (minus-plus) and abnormal deeply inverted T_2 and T_3. Comment: This is a grossly abnormal electrocardiogram indicating severe cardiac damage. Possibilities might include a severe toxic myocarditis or a marked anoxemia of the myocardium."

The course of this infant's illness seemed to us almost entirely in keeping with classical amyotonia congenita of the Oppenheim type. The weakness and hypotonia progressed to the point where respiratory movements were weak, breathing became largely abdominal, and pneumonia developed. The outstanding features which did not fit into this disease entity were the macroglossia present from birth, the marked cardiac enlargement and electrocardiographic changes, and the enlarged liver, presumably due to heart failure, first low-grade and chronic and terminally severe.

MORBID ANATOMY

At autopsy, performed four hours after death, the greater part of the thorax was seen to be occupied by the tremendously enlarged heart which encroached principally on the left pleural space, reducing most of the left lung to a thin atelectatic ribbon. The liver extended 4.5 cm. below the right costal margin at the mid-clavicular line. The relations of the other viscera and their positions were not unusual.

Heart.—The heart weighed 110 grams (normal weight 32 grams). It was uniformly hypertrophied, and had a rounded contour. The massive myocardium was very firm, pale grayish pink in color, and its cut surface was of glassy, homogeneous texture. The left ventricular wall averaged 19 mm. in thickness, and the right ventricle was 16 mm. thick. The interventricular septum was also exceedingly thick, and the papillary muscles as well as the atrial walls appeared conspicuously hypertrophied. There were no septal defects, the great vessels and coronary arteries were normal in course and origin, and the valves were of normal configuration.

In the microscopical sections the myocardium presents the arresting appearance of a meshwork of round, oval, or elongated lattices, as seen in the usual preparation. This is due to the peripheral displacement of the cytoplasm and the myofibrils of the fiber by a large central vacuole. In hematoxylin and eosin preparations the muscle fiber thus appears as a distended hollow cylinder with thin delicately cross-striated walls enclosing a large empty space. Very few myocardial fibers are spared, and the enlarged muscle bundles are closely packed together, compressing the interstitial tissue (Fig. 4). That the vacuoles contain glycogen is well demonstrated in sections of blocks fixed at once in Rossman's fluid and stained according to the method of Bauer, for glycogen. Large magenta colored masses and granules, representing glycogen, solidly fill the central spaces of most of the fibers (Fig. 5). Diastase digestion completely removes the stainable material, establishing the specificity of the staining reaction.

Lungs.—The base of the upper lobe and the lower lobe of the right lung were dark red, firm, and airless, in contrast to the pink crepitant apical parts. The compressed atelectatic midsection of the left lung, comprising the greater part of the lower lobe and the base of the upper, was a thin strip of livid hue.

Microscopically, both lungs are found to be the seat of an acute pneumonia, and the typical picture of atelectasis is found in the left lung. The musculature of the bronchi and arteries in the sections appears very pale, hypertrophied, and in cross-section each fiber is seen to be swollen and contains

a large clear central vacuole. These vacuoles are seen to be filled with stained masses (glycogen) in formalin-fixed material prepared with Bauer's technique.

Liver.—The liver weighed 295 grams (normal weight 195 grams). It was enlarged, and on cut section its substance appeared very pale tawny pink, of solid consistency and homogeneous texture in which no lobular architecture was discerned.

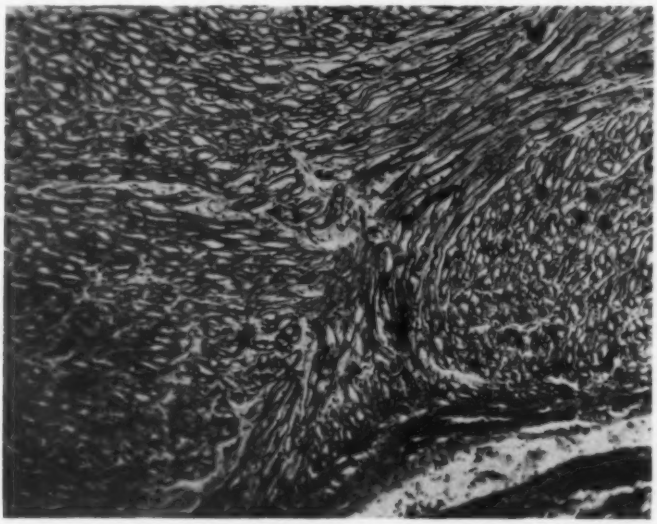


Fig. 4.—Myocardium, with characteristic vacuolation of the cardiac muscle fibers resulting in the histiologic appearance of a latticework composed of hollow cylinders with thin, faintly striated walls. (Zenker fixed, hematoxylin and eosin stain, ×100.)

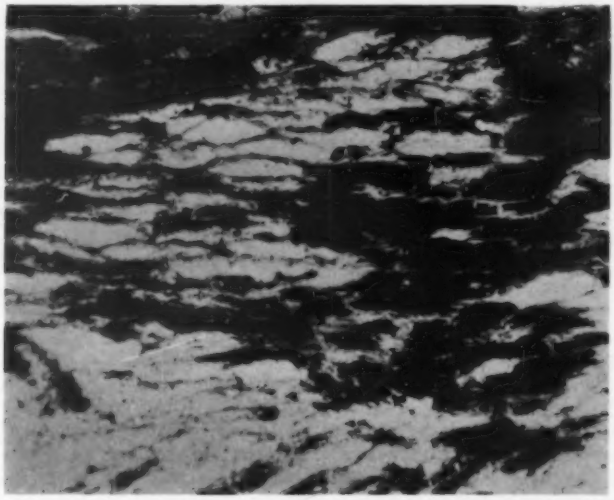


Fig. 5.—Glycogen masses in cardiac muscle fibers, shown as dense clumps occupying the central space of the fiber. In some areas, the glycogen has fallen out, leaving empty spaces enclosed by delicate, distended sheaths in which small granules of glycogen remain. (Rossman fixed, Bauer method, ×450.)

Histologic sections stained with hematoxylin and eosin show the parenchyma to be formed of compact masses of large polygonal cells arranged in solid cords whose disposition into definite lobules is hard to make out. The cellular cytoplasm is finely vacuolated, appearing foamy. The nuclei remain central. The sinusoids are compressed by the massive cords, the von Kupffer cells being on that account difficult to distinguish. Bauer's stain for glycogen applied to Rossman fluid-fixed blocks reveals the presence of large magenta colored, diastase digestible masses within the enlarged liver cells. While the sections resemble those obtained at biopsy or from experimental animals given carbohydrates, the appearance of so much glycogen in post-mortem liver from a child who had been febrile must be regarded as abnormal, and evidence of its unusual fixity due to a failure of post-mortem glycogenolysis. There is no increase of Sudan stainable material.

Pancreas.—The acinar cells of the pancreas contain numerous clear vacuoles giving them a reticulated foamy appearance. The duct epithelium is composed of unusually large pale cells. There is numerical and dimensional increase of islet tissue in the sections examined, but general conclusions respecting the total islet tissue are probably not warranted on this basis.

Kidneys.—The right kidney weighed 26 grams, and the left 25 grams, being within normal limits. In hematoxylin and eosin-stained sections the cells of many of the distal convoluted tubules and ascending limbs of Henle's loop, and all of the collecting tubules, as well as those composing the epithelium of the renal pelvis, are swollen, very pale, and enclose clear vacuoles.

With Bauer's technique on material fixed in Rossman's fluid a diffuse coloration appears in the glomeruli, and scarlet granules are revealed in some of the cells of the distal convoluted tubules, ascending limbs of Henle's loop, and in almost all of the cells of the collecting tubules and pelvic epithelium. The stained material represents diastase digestible glycogen. There is no increase of histologically demonstrable fat.

Spleen.—The cells of the conspicuous germinal centers of the Malpighian corpuscles and many large cells in the red pulp appear unusually large and have abundant frothy cytoplasm, as seen in the usual hematoxylin-eosin preparations. The sinusoids of the spleen are compressed and inconspicuous.

Thymus.—Bauer-stained preparations of blocks fixed in Rossman's fluid reveal the presence at close intervals of reticulum cells swollen with glycogen-containing vacuoles.

Endocrine Organs.—The thyroid gland weighed 5 grams (within normal limits). Microscopically, it is composed of small colloid-containing acini of usual appearance.

The adrenals weighed 6 grams together (normal average weight 4 grams). In preparations, the cortex, which is demarcated into the usual zones, is very pallid due to the glycogen content of its cells, as demonstrated with Bauer's stain even after fifteen weeks in formalin.

Smooth Muscle.—In hematoxylin and eosin preparations the smooth muscle in the media of the muscular arteries, the bronchi, intestine, and urinary bladder has a very pallid appearance due to the presence of large, clear, axial vacuoles in the muscle fibers which have become enlarged. The sarcoplasm, myofibrils, and nucleus are pushed peripherally by central glycogen masses which are revealed in Bauer- or carmine-stained sections.

Striate Muscle.—Histologic sections through the psoas, spinati, quadriceps, tongue, and diaphragm show an unusual series of changes. The muscle fibers are involved in varying degree in a unique form of vacuolar change with the formation of peculiar basophilic material. The progression of this remarkable injury can be followed serially, and will be dealt with in greater detail in a

subsequent communication. Briefly, the myofibrils become separated into compacted bundles by the growth of elongated axial vacuoles, presumably glycogen-containing, which come to form longitudinal cleavage planes within the fiber. Tinctorial changes then become manifest in some of the myofibrils, as segments of them become uniformly basophilic, while at the same time rounded basophilic

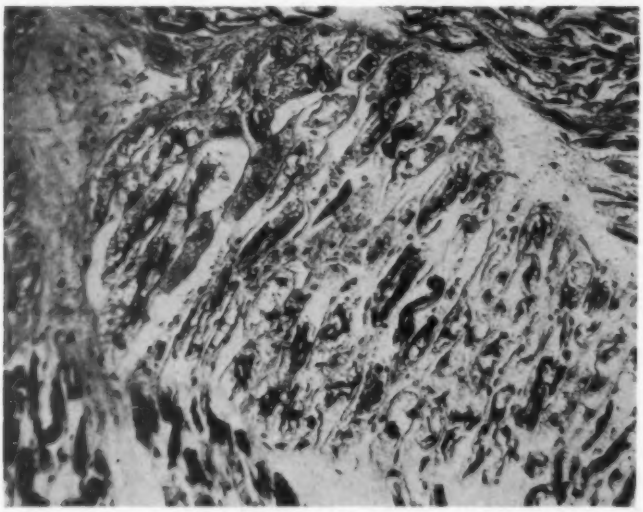


Fig. 6.—Tongue muscle, with a bundle showing advanced vacuolation and degeneration of fibers, characterized by the presence of basophilic material within the sarcolemma. (Zenker fixed, hematoxylin and eosin stain, × 250.)

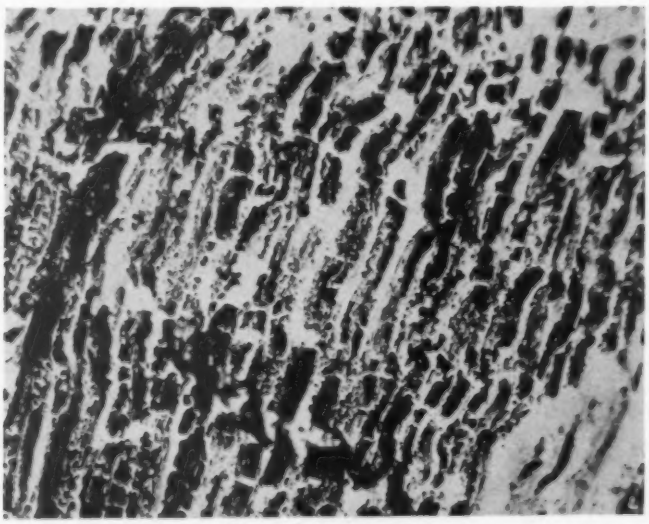


Fig. 7.—Glycogen in striated muscle, disposed as granules, rodlets, clumps, or larger masses in and between the myofibrils, in greatly increased amount. (Rossman fixed, Bauer method, ×250.)

refractile bodies and granules (as shown with methylene blue), appear in the spaces between the myofibril bundles. As more fibrils become involved and disintegrate, the myofibril bundles become thinner and fewer, and the space within the ballooned sarcolemmal sheath becomes filled with basophilic granules, outlined refractile bodies, and networks of beaded threads. (Fig. 6.) Thus in proportion as the myofibrils degenerate, the sarcolemmal sheath becomes filled with basophilic material which then tends to disappear as the process continues, leaving finally a distended nearly empty sarcolemmal sheath in which lie pyknotic nuclei which have moved toward the center away from the sarcolemma, surrounded by granular cytoplasmic (perinuclear) masses with bridging process. The involved fiber may be affected entirely or segmentally. Stains for glycogen make apparent dense masses and granules (glycogen) lying within and between the fibrils of all the fibers. (Fig. 7.) The basophilic substance described also takes these stains.

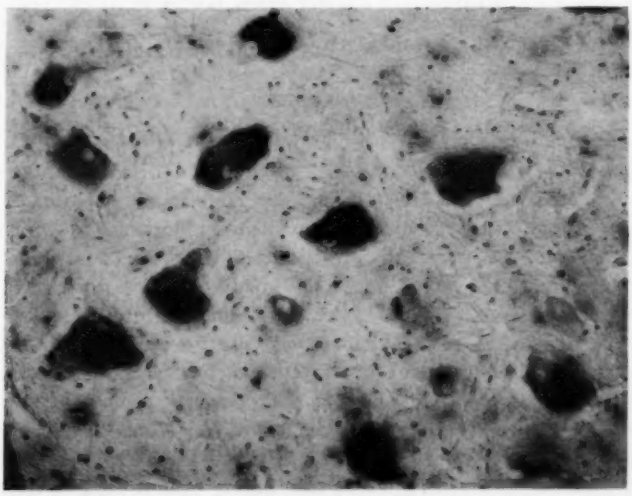


Fig. 8.—Swollen anterior horn neurons of the spinal cord whose centers are occupied by glycogen, seen as dark material which has diffused beyond the confines of the central vacuole. The nucleus is displaced peripherally. (Formalin fixed, Bauer method for glycogen, ×250.)

Central Nervous System.—Sections taken from frontal cortex hippocampus, region of the basal ganglia and internal capsule, pons, medulla, cerebellum, cervical and lumbar cord were examined after a seven-day sojourn in 10 per cent formalin.

The ganglion cells comprising the cerebellar dentate nucleus, all of the stem nuclei of medulla and pons, and the neurons of the ventral and lateral horns of the cord and isolated neurones in the basal ganglia are similarly altered. The cytons of these nerve cells are swollen, some to two or three times the normal size, and appear very pale. In hematoxylin-eosin or Nissl-stained sections the cytoplasm seems to form a thin compressed peripheral rim enclosing a large unstained vacuole which occupies the center of the cell and displaces the nucleus and the chromidial substance peripherally. Stains for glycogen reveal its presence in the central part of the swollen neurones (Fig. 8). In Bielschowsky preparations the neurofibrillar pattern of these affected neurons is seen to be distorted and the fibrils displaced. Apparently only those neurone

groups listed are affected, and these are involved in about the same degree. Varying numbers of astrocytes of the cerebral cortex hippocampal region, and thalamus are filled with glycogen and are beautifully delineated down to their finest ramifications, by Best's carmine.

Chemical Analysis.—Analyses for glycogen are reported as follows in terms of wet weights:

Heart (fixed in absolute alcohol)	3.0 grams per cent
Heart (fixed in formalin twelve hours)	4.8 grams per cent
Liver (fixed in absolute alcohol)	0.38 gram per cent
Striated muscle (fixed in formalin twelve hours)	2.2 grams per cent

The figures given by van Creveld[6] for the glycogen content of various organs of an infant with marked idiopathic hypertrophy of both ventricles, who had passed through a period of fever before death, are reproduced below for comparison:

Heart	0.055 gram per cent
Liver	0.103 gram per cent
Muscle	0.011 gram per cent

DISCUSSION

Types and Incidence of Glycogen Disease

In general at least two main types of glycogen disease, having different clinical characteristics, are recognized: the hepatic or hepatonephromegalic described by E. von Gierke,[11] and the cardiomuscular type, in which the preponderant deposits of glycogen are in the heart or heart and striated muscle.[6-8, 10, 12] A third group in which involvement of the central nervous system predominates was suggested by Antopol, Heilbrunn, and Tuchman.[13] Although the rigidity of such classifications into pure types cannot always be maintained, since some anatomic overlapping is usual and clinical borderline forms, such as the case of Kimmelstiel,[2] may possibly occur, they nevertheless serve a definite clinical usefulness. Common to all forms of glycogen disease is the excessive accumulation in the cells of the affected organ system of quantities of glycogen of unusual apparent stability in that it fails to undergo postmortem autolysis at the usual rate.[2, 6, 8, 9, 15-17, 21] The glycogen is of normal composition,[17] and can be split readily by diastase, normal liver, or normal heart.[6, 8, 9, 15] The basic defect is believed to be a failure of glycogenolysis, resulting in the accumulation of glycogen.

Of some 200 cases of this disease which have been reported since its description in 1929, about 50 are said to have satisfied those clinical or pathologic criteria such as have been proposed by Mason and Anderson,[8] and Bridge and Holt.[9] Some 27 cases of cardiomegalia glycogenica have been submitted heretofore, and of these 19 had been proved chemically or histochemically previous to 1948 (Sprague, Bland and White 1[18]; Putschar, Bischoff 1[19]; Pompe 3[20]; Humphreys and Kato 3[12]; Antopol, Heilbrunn and Tuchman 1[13]; Hertz and Jeckeln 1[21]; Wolff 1[22]; Mutgeert, Mansens 1[23]; Gardner and Simpson 1[24]; van Creveld 1[6]; Günther 1[14]; Antopol, Boas, Levison, and Tuchman 1[25]; Bonaba, Saldun de Rodriguez, and Ferreira Berrutti 1[26]; Schneider, Scheidegger 1[4]; Wachstein 1[5]).

Clinico-Pathological Correlation in Patient Reported

The case here reported is the twentieth proved case of glycogen disease of the cardiomuscular type. It is noteworthy not only for the diagnostic problem it presents, but also for its extraordinary clinical manifestations, many of which are readily correlated with the anatomical picture. The features which led to the clinical impression of infantile myxedema are not based on any demonstrable abnormality in the thyroid or pituitary glands. The striking macroglossia was apparently due to the peculiar degenerative changes in the tongue musculature consequent on massive glycogen deposition in its fibers. When at the age of 4 months hypotonia and muscular flaccidity became so outstanding a part of the symptom complex, a diagnosis of amyotonia congenita was accepted. These manifestations can be related to both the grave skeletal muscle and the motor neuron injury which occurs with the deposition of glycogen. It is difficult to know in what proportion the lesions in each of these systems contributed towards the clinical picture of amyotonia congenita, for there is histologic evidence that the functions of both muscle and nerve cells were seriously impaired. Single muscle fibers in which there is relatively early vacuolation and separation of myofibrillar bundles are found folded or pleated in such a way as to suggest a loss of contractility and their passive crumpling by intact, active adjacent fibers. In the altered nerve cells, special preparations reveal some structural disorganization of the neurofibrillar network. The protuberant belly and umbilical hernia may likewise reflect the intrinsic disease of the muscle, with weakening of the abdominal musculature.

The Heart

Cardiac enlargement was noticed roentgenologically in this case three and one-half months after birth, but the nature of the heart disease remained obscure during life. Symptoms of congestive heart failure were not prominent. Hypertrophy of the heart is said to be found often in children who are without particular complaints at birth and who may remain without symptoms until shortly before death. Indeed, Gardner and Simpson[24] have described sudden death due to glycogen disease of the heart in children previously asymptomatic. Symptoms of congestive heart failure do not usually constitute prominent features in the clinical course. When cardiac insufficiency occurs, it appears most often to develop rapidly and terminally. The occurrence of chronic congestive failure may be related to advanced degenerative changes in the myocardium with fibrosis, after glycogen accumulation of long standing, as in the unusual case of Antopol, Boas, Levinson, and Tuchman in which chronic severe congestive heart failure was the outstanding clinical feature.[25]

Evidence of myocardial injury during life may also be found in electrocardiographic tracings, which are of particular interest in this condition, and of which only three, besides the present one, have been published in proved cases of cardiomegalia glycogenica.[18, 23, 25] In the present instance, the electrocardiogram, taken on the day of death, showed evidences of severe cardiac

damage, with high voltage, deep Q_2 and Q_3, depressed RST, and inverted abnormal T_2 and T_3.

In 1931, Sprague, Bland, and White[18] reproduced a tracing from their case, subsequently verified as a case of cardiac glycogenosis, showing only sino-auricular tachycardia and a normal electrical axis. Mutgeert's case of 1936[23a] exhibited the following changes: in Lead I, P waves split at crest, T inverted; in Lead II, P waves split at crest, T inverted and diphasic; in Lead III, deep Q, positive T wave. The PR interval was 0.10 seconds, and no deviation of the electrical axis was present. This tracing, therefore, gives evidence, especially in the T-wave changes, of myocardial disease. Particular involvement of the conduction system of the heart has been observed anatomically by Putschar,[19a] by Humphreys and Kato,[12] and by Wolff,[22] and this may find expression in conduction disturbances such as the left bundle branch block recorded in the case of Antopol, Boas, Levison, and Tuchman.[25] These authors, however, were unable to differentiate the conduction system histologically. Electric axis deviation as such has not been seen, and indeed the uniform kind of myocardial hypertrophy which occurs in cases of diffuse cardiac glycogenosis would by itself hardly be expected to determine an axis preponderance.

Clinical Course

The final events leading to the death of this baby (D. B.), with rapid onset of fever and pneumonia, form the most common terminal episode in cardiomegalia glycogenica, having been recorded in at least ten of the known cases. The compression atelectasis particularly of the left lung by the tremendously enlarged heart, as in the present case, undoubtedly plays a large part in the development of the pneumonia.

In only two instances of known cardiac glycogen disease did the affected children survive beyond the first year: Gardner and Simpson's case occurred in an 11-year-old boy who died suddenly,[24] and Antopol, Boas, Levison, and Tuchman[25] reported a case in a 15-year-old boy who died in progressive heart failure. Excluding these, the average age of death lies at about 6 months. Death, then, is most often the result of cardiac insufficiency and acute, usually pneumonic, infection.

A New Diagnostic Subtype of Cardiomuscular Glycogen Disease

The cardiac form of glycogen disease has not so far been definitely diagnosed during life, in contrast to the hepatic form of the disease, for which well-defined clinical diagnostic criteria exist.[8, 9] These are based on the marked hepatomegaly, infantilism and underdevelopment, fasting hypoglycemia and ketosis, adrenalin resistance and insulin sensitivity, and abnormal glucose tolerance curve which occur in the hepatic type of glycogen disease. These physiologic disturbances have their common origin in a congenital defect in the enzymatic breakdown of glycogen to glucose by the liver in particular, with consequent accumulation of glycogen.[6, 8, 9, 16] Symptoms reflecting such general metabolic disturbances are unknown in the cardiomuscular type of glycogen disease,

a syndrome due to a congenital defect manifested in early infancy, whose symptomatology is related only to the consequences of localized deposits of glycogen, and which almost always results in death during the first year.[6, 8, 9] The absence of fasting hypoglycemia and ketonuria in this latter group of cases has been stressed.[6, 12]

In the case here recorded, we appear to be dealing with a particular subtype of the cardiomuscular form of glycogen disease presenting a definite clinical syndrome with characteristic features typical of infantile myxedema, mongolism, and later, of amyotonia congenita. The general underdevelopment with cretinoid or mongoloid facies and habitus, the umbilical hernia, the dry, turgid skin, the enlarged, protruding tongue, the hypotonia and sometimes listlessness, feeding difficulties, respiratory distress, and possibly subnormal temperature[21] lead inevitably to the impression of infantile myxedema. Muscular flaccidity may dominate the picture as its most outstanding feature, which may have most of the clinical qualifications of amyotonia congenita.

Comparable Cases From the Literature

The literature records at least two instances[18, 21] in which a diagnosis of hypothyroidism was made in cases subsequently proved at autopsy to be cardiomegalic glycogen disease, and in three other instances[4, 14, 22] hypotonia was marked, sufficiently to lead to a consideration of amyotonia congenita in one.[14]

Sprague, Bland, and White[18] reported a case in 1931 occurring in a 7-month-old girl in which a tentative diagnosis of thyroid hypofunction was made because of dry skin, large protruding tongue, and hypotonicity. This case was subsequently proved by Tracy Mallory (1934) to be an instance of cardiomegalia glycogenica.

In 1936 Hertz and Jeckeln[21] drew attention to the remarkable appearance under which this type of glycogenosis may be disguised. In their case, that of a 5-week-old female infant, the myxedematous facies was so outspoken as to leave "no doubt as to the diagnosis." The enlarged protruding tongue gave rise in their case to great difficulty in nursing and breathing. Hypotonia was extreme: "the child lay quite motionless and hardly reacted to touch." This may conceivably have contributed to the subnormal temperature (34° C.) which was observed. The infant finally died of erysipelas and meningitis. At necropsy the heart was found to be enlarged to about twice the normal size, and had the typical histologic appearance of glycogenosis, with demonstrable glycogen deposits. The liver, smooth muscle, endothelium, thymus, kidney, and some ganglion cells were also involved in lesser degree, and vacuolar degeneration of striated muscle, most marked in the tongue, was reported. There was no definite glandular abnormality.

Injury to the striated muscle may also find expression in related symptoms, as was indicated in the case here presented. Wolff (1936),[22] in a communication describing in some detail the morphology of the striated muscle degeneration of glycogen disease, reported a case occurring in a 5-month-old girl with outstanding enlargement of the tongue and clinical manifestations of cardiac

insufficiency. In addition to glycogenic cardiomegaly, the liver, smooth muscle, endothelium, spleen, kidneys, and lungs were shown to be the sites of glycogen deposition. The endocrine glands were intact. The striated muscle injury was observed to be most advanced in the tongue.

The first observations on this peculiar vacuolar basophilic degeneration, which is unique in the pathology of muscle, were made by Humphreys and Kato in 1934[12] on their first and third cases. Further contributions toward an understanding of the pathologic anatomy of the remarkable changes occurring in the striated muscles were made by Günther.[14] In 1939 she reported the case of an 11-month-old child who was apparently well until three months before death, at which time hypotonia and listlessness became increasingly evident and a diagnosis of amyotonia congenita was made. The child died of pneumonia. A 2-year-old sibling is said to have died under similar circumstances. At autopsy the heart was found to weigh 75 grams (normal 40 grams) and its musculature, as well as the parenchyma of the liver, and the smooth muscle showed the typical histologic changes of glycogen storage. The morphogenesis of the changes in the striated muscle, which were essentially similar in degree to those noted by Wolff[22] and by the present authors, were detailed by Günther. Vacuolar degeneration of striated muscle in varying degree has been observed in seven instances, including the present one[6, 12, 14, 21, 22] and glycogen deposition in striated muscle without advanced injury seen in additional cases.[2, 4, 5, 20, 25] The tongue was particularly involved in three of these cases previously reported,[4, 21, 22] leading to its enlargement. All the cases of severe striated muscle glycogenosis occur together with cardiac involvement, but in only one instance[25] has basophilic change of the myocardium been seen. Significantly, in both Günther's case[14] and in the present one the motor ganglion cells of the anterior horn of the cord were swollen by glycogen vacuoles; in both cases there were identical changes in muscle and nerve, and both were diagnosed as cases of amyotonia congenita during life.

Glycogen deposits were observed by Schneider[4a] and Scheidegger[4b] in the ganglion cells and glia of the cortex of a 9-month-old boy with marked muscular hypotonia, who died after a very brief course. Glycogen accumulations were also present in the kidney, liver, and striated muscle, the latter apparently being responsible for a mild lingual hypertrophy. Peculiar globular intracellular inclusions were found in the ganglion cells, some of which showed abnormal forms. In addition to the cases of Günther[14] and Schneider,[4] which have been referred to, the patients of Kimmelstiel,[2] Hertz and Jeckeln,[21] von Creveld,[6] and Wachstein,[5] as well as our patient, all of whom had cardiac glycogenosis, are reported to show glycogen deposits in the central nervous system. This has also been observed in at least two cases of hepatomegalic glycogen disease.[3, 8] Antopol, Heilbrunn, and Tuchman[13] are ready to accept as a main type of glycogen disease that category in which central nervous system involvement predominates, and these authors suggest that poorly understood cerebral conditions in children should be reviewed in order to determine whether some of them are not related to the effect of abnormal glycogen storage. This classi-

fication, which includes neural glycogenosis as one of three principal forms, remains to be justified by further experience.[6, 22] It would seem, from information now available, that most cases of marked nervous system glycogenosis also suffer from the cardiomuscular type of glycogen disease, which constitutes the predominant type.

That our case (D. B.), together with those of Sprague, Bland, and White,[18] Hertz and Jeckeln,[21] Wolff,[22] Günther,[14] and perhaps Case 1 of Humphreys and Kato[12] constitute a definite subtype of cardiomuscular glycogen disease would seem to us apparent. The existence of a special subtype of the cardiac form of glycogen disease, in which there is a myxedema-like clinical picture has also been recognized by Schneider,[4a]

Any child under one year of age, presenting features of infantile myxedema with prominent tongue and/or marked muscular hypotonia, and who is found to have an enlarged heart, should be suspected of having cardiomuscular glycogen disease with possible central nervous system involvement. Additional weight is given to this impression if hepatomegaly be found, and confirmation of the diagnosis may be obtained during life by muscle biopsy. A further clinical test which might prove helpful in confirming the diagnosis would be the failure of the blood lactic acid to rise sufficiently after the injection of epinephrine.

In none of these cases has any important morbid change been noted anatomically in the thyroid or pituitary glands. There thus appears to be no question of a true hypothyroid condition or other endocrinopathy. Rather the similarities represent a coincidence of certain clinical manifestations which are dependent, in the case of hypothyroidism, largely upon the myxedematous infiltration of muscles (particularly tongue) of the myocardium, skin, respiratory and alimentary tracts, etc., and in the case of glycogen disease upon massive deposits of glycogen in the myocardium, striated muscle, particularly the tongue, the nervous system, and smooth muscle, with more or less injury.

Pathology

The pathology of glycogen disease will be more completely commented upon in a subsequent communication. At this point it is only necessary to indicate that in cases of the cardiac type of glycogen disease there has been found at one time or another, in addition to glycogenosis of the heart, glycogen accumulations in nearly all the organs studied, which is almost the same state of affairs as in the hepatic type of glycogen disease. The other involved organs may or may not be enlarged, but there is always present in them an accumulation of glycogen typically resistant to post-mortem breakdown. The existence of separate hepatic and cardiac forms of glycogen disease as distinct entities which, when pure, are clinically and pathologically different can hardly be doubted. Mixed cases, however, showing features of both, may rarely occur, and we have such an instance in Kimmelstiel's case.[2] Moreover, individual cases, particularly of the cardiomuscular form, can show a varied picture, not only with respect to the distribution of glycogen among the different organs but in the deposi-

tion of glycogen in the cells. In this connection it may be noted that glycogen storage has been found in the reticuloendothelial system in a number of cases,[5, 20, 22] refuting the opinion expressed by Kimmelstiel[2a] that glycogen disease differs essentially from the lipoidoses in its failure to involve the reticuloendothelial system.

Pathogenesis

Concerning the pathogenesis of von Gierke's disease, many theories have been proposed. Those advanced prior to 1939 are summarized in van Creveld's exhaustive review.[6] However, before there was a more complete understanding of the series of steps involved in enzymatic glycogenolysis, the problem could not be dealt with adequately. The concept that "true" or "primary" glycogen disease represents a heritable and therefore inborn defect in one of the steps in the enzymatic chain of reactions concerned in glycogenolysis is the hypothesis most consistent with the known facts.[8, 9, 27] It would also appear reasonable for theoretic reasons to suppose that the specific locus of this defect in the series of enzymatic reactions differs in the hepatic and in the cardiomuscular forms. "Primary" or "true" glycogen disease should be distinguished, at least with respect to its etiology, from the picture of large glycogen deposits secondary to or incident upon such conditions as newborn infants of diabetic mothers and/or erythroblastosis fetalis, which conditions may occasionally present a picture very similar to cardiomuscular glycogen disease, but always show pancreatic islet hyperplasia.[28, 29] "Primary" glycogen disease would, therefore, be another example of those genetically determined metabolic anomalies which have as their basis a deficiency of some enzyme component in a concatenated series of intracellular enzymatic reactions involved in metabolism; in this case of glycogen, glucose, and their phosphoryllated intermediaries. In hepatomegalic glycogenosis this defect may well reside in the liver alkaline phosphatase.[27] There is yet no indication of the enzymatic locus of the disturbance in cardiomuscular glycogen disease.

Heredity

The heredity of glycogen disease and the possible genetic mechanisms involved have long been under examination. Although most cases have seemingly occurred as isolated examples, a sufficient number of cases with a familial incidence or with histories of parental consanguinity have been described to give impressive testimony to the concept of the heritability of glycogen disease. Thus, a familial incidence has been noted in the cases of Sprague, Bland, and White,[18] Ellis and Payne,[16] Unshelm,[2b] Günther,[14] and particularly Abramson and Kurtz[30] and by other authors. Two of these cases were of the cardiomuscular type. Consanguinity of the parents (cousin marriages) has been noted particularly in the cases of Unshelm,[2b] van Creveld,[6] and Ellis and Payne,[16] information which points to inheritance as a simple recessive gene.[31] There is apparently no sex-linkage. Hanhart has treated the subject of the heredity of glycogen disease on the basis of his analysis of twenty-one cases, and also notes

a heritable factor.[32] If the conclusions supported by these facts, admittedly drawn from relatively few cases, are correct, then the chances of a couple who have had a child with von Gierke's disease, of having another affected infant are high (presumably one out of four will have the disease) and the risk must be taken into careful account.

Prognosis

The prognosis of cardiomegalis glycogenica, in marked contradistinction to the hepatic type which has relatively a much better prospect, would appear to be uniformly fatal, and all but two of the known cases of cardiomuscular glycogen disease died before their first year. Since, however, this form of the disease has never been clinically diagnosed, and since all the available information has come from autopsy data, the actual incidence and prognosis of cases cannot be fairly evaluated. The occurrence of two cases in boys who have survived to the ages of 15 years,[25] and 11 years[24] is at least suggestive that some may possibly remain unrecognized or may be of mild character, and that conceivably the actual outlook in cardiac glycogenosis may not in all cases be completely hopeless.

SUMMARY

1. An infant who succumbed at 6 months of age to the cardiomuscular type of glycogen storage disease is reported, the twentieth such patient in the literature.

2. The features which strongly resembled both cretinism and mongolism early in her course are described, as well as the reasons for the final ante-mortem diagnosis of amyotonia congenita.

3. A close correlation between clinical signs and pathologic findings is found.

4. Evidence presented and literature reviewed suggest that the patient represents a definite subtype of the cardiac variety of glycogen disease in which glycogen deposition in the central nervous system is a prominent feature.

5. It is suggested that glycogen disease should be strongly considered when a young infant is encountered who presents the clinical picture of cretinism with macroglossia, marked generalized muscle hypotonia, and cardiac enlargement.

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THE USE OF POSITIVE PRESSURE AS AN AID IN THE HANDLING OF RESPIRATORY PARALYSIS FROM ANTERIOR POLIOMYELITIS

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DURING the past few years there has developed increasing evidence of the value of positive pressure in the treatment of pulmonary disease. Portable positive pressure respirators[1] have been developed, and the principles underlying the use of positive pressure have been outlined.[2, 3] Positive pressure resistance breathing has been used in patients with poliomyelitis in conjunction with a tracheotomy.[4] However, very little has been said about the use of positive pressure breathing in patients with bulborespiratory poliomyelitis in whom tracheotomies have not been done. Our experience suggests that the positive pressure respirator has two areas of usefulness in handling patients suffering from respiratory paralysis due to this disease.

The first of these is in moving patients from one tank type respirator to another or in opening the respirator for purposes of administering intravenous fluids, taking x-rays, and for certain nursing procedures. Especially in small children the administration of intravenous fluids is difficult while the patient is in a respirator. By using a portable positive pressure respirator it is possible to obtain adequate ventilation while the respirator is open for periods of fifteen or twenty minutes, or however long is required to start intravenous fluids or to carry out other necessary procedures.

The second field of usefulness is in the treatment and prevention of pulmonary edema developing during the course of respiratory paralysis. A large proportion of those children who develop respiratory paralysis subsequently experience progressive difficulty with air exchange after being placed in the standard respirator. It has been felt that the problem was one of the accumulation of secretion in the bronchi, and to combat this, postural drainage and bronchoscopy have been used. Although bronchoscopy and tracheotomy are definitely indicated in some patients, results with these forms of treatment alone have been discouraging. Frequently bronchoscopy of patients who have shown progressive pulmonary hypoventilation fails to reveal a definite plug responsible for the apparent atelectasis. X-ray examination may reveal a diffuse process rather than a lobar one, and following bronchoscopy the patients frequently are worse than they were prior to the procedure. It is our belief that in many instances the progressive hypoventilation which develops in the paralyzed patient is due to pulmonary edema rather than to atelectasis. In patients of this type we have found that the intermittent use of positive pressure breathing leads to improvement.

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There are probably several factors which lead to the development of pulmonary edema in poliomyelitis. A frequent one is anoxia, which, by its action both on pulmonary capillaries and in the central nervous system, may cause changes in capillary permeability leading to pulmonary edema. Another factor is stasis due to the difficulty in changing a patient's position in the standard respirators. A third factor may be the development of negative pressures within the alveoli. It should be emphasized that any obstruction of the airway, from the mouth to the alveolus, in a patient in a respirator will lead to the development of negative pressures within the alveolus and will encourage pulmonary edema. Finally, there is a possibility that in certain cases of poliomyelitis, the central nervous system lesion itself may produce pulmonary edema directly through some vasomotor disturbances.[5]

If pulmonary edema is to be prevented, active measures must be instituted from the beginning in all cases developing respiratory embarrassment. These measures include (1) the liberal use of oxygen; (2) repeated (every two hours) changes in body position from back lying to face lying (the tilting provided in the respirator is insufficient); (3) the intermittent use of positive pressure breathing, approximately fifteen minutes every one to two hours. This should be instituted early and continued as a prophylactic measure in all acute cases during the first few days and thereafter as needed to combat pulmonary edema. These measures serve to counteract anoxia, to prevent stasis, and to combat pulmonary edema directly by the establishment of intermittent positive pressures within the alveoli.[6]

It should be pointed out that in using a positive pressure respirator (and, in fact, any time that one is administering 100 per cent oxygen) the oximeter is an unreliable index of pulmonary ventilation. Once the lungs have been filled with oxygen, it requires extremely little ventilation to maintan adequate blood oxygen saturation, yet dangerously high levels of carbon dioxide may be established. Preliminary observations have confirmed the existence of high carbon dioxide levels in some of our cases. An oximeter reading showing a good saturation may give a false sense of security under these circumstances. However, an easy method of obtaining a rough measure of pulmonary gas exchange when using the positive pressure respirator is to observe the oximeter reading when the respirator is connected to a cylinder of compressed air instead of oxygen. Under these conditions, the oximeter reading does give a fairly reliable indication of pulmonary gas exchange.

During the 1948 epidemic in North Carolina we had the opportunity to use positive pressure breathing in ten patients with the respiratory or bulborespiratory form of poliomyelitis.* In three instances severe pulmonary edema was reversed by the use of the positive pressure respirator, and in some of the others we feel that pulmonary edema was prevented. An example of the most severe case follows:

O. T. was a 6-year-old girl admitted July 25, 1948, with acute poliomyelitis of three days' duration. There was a steady progression of spinal and

*The apparatus used in these cases was obtained from Mine Safety Appliances Co.

respiratory involvement which necessitated the use of the Emerson respirator on July 27. At this time there was extensive paralysis of all extremities and of the intercostal muscles. Minimal difficulty in swallowing was experienced. The child improved after being in the respirator and was alert. On July 31 she developed a severe acute hemolytic anemia, presumably due to her treatment with phenosulfazole. She recovered from this and became alert again. On August 3 she became less alert, and oximeter readings showed a gradual drop in the oxygen saturation of the blood, despite the use of oxygen in addition to the respirator. There was diminished respiratory excursions as gauged by listening over the nose and mouth. X-ray examination of the chest showed a diffuse shadow, presumably due to atelectasis of the left lower lobe. This increased to involve the entire left lung. Laryngoscopy showed a normal larynx,

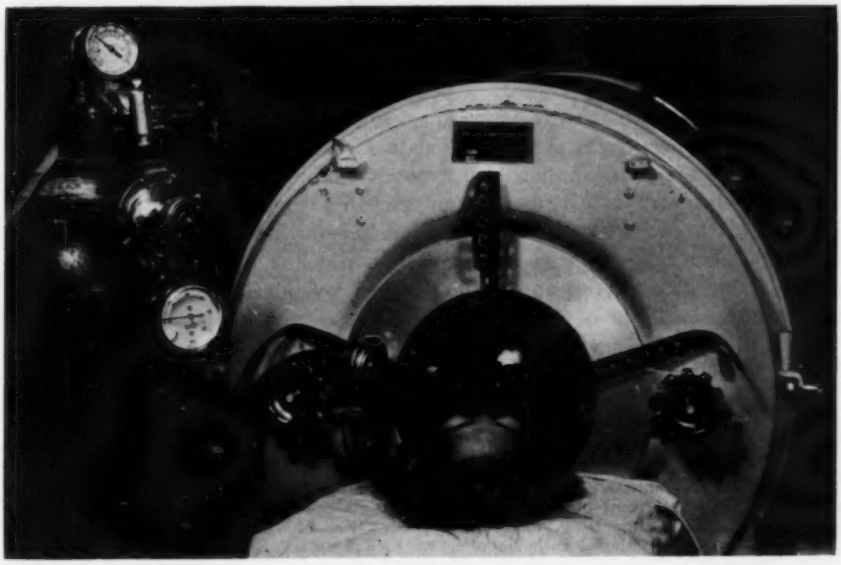

Fig. 1.—Patient getting intermittent positive pressure breathing with oxygen while respirator is open.

and bronchoscopy with suction revealed no definite plugging of the left bronchial tree. Very little mucus was obtained. No improvement in air exchange was noted with the bronchoscope in place. Following the removal of the bronchoscope the patient became much worse. Cyanosis occurred and mucous accumulated in the throat. At this time intermittent positive pressure breathing was instituted for approximately five minutes in every hour. There was temporary improvement, but on August 4 the child again became unresponsive and cyanotic and the respiratory exchange became minimal. X-ray continued to show a picture compatible with atelectasis of the left lung. Because of the patient's precarious state and the previous reaction to bronchoscopy, it was decided to

use intermittent positive pressure breathing with pure oxygen alternating with the respirator every thirty minutes. On this regime, respiratory exchange improved, and by Aug. 5, 1948, the patient was responding to questions. Improvement continued, and on August 7 x-ray of the chest was negative, and the patient began making shallow unaided respirations. By August 9 she could get along for five to eight minutes with unaided breathing. She had not been able to swallow more than sips of fluids and had been carried along on parenteral and rectal fluids. However, on August 9 gavage feedings were instituted. In general she was doing quite well with positive pressure breathing for thirty minutes every two hours until August 11, when she again showed poor blood oxygenation, even with oxygen by mask while in the respirator. She did not seem in poor condition, however, and gavage feedings were continued. On August 11, just as the first of a feeding was being given by gavage, she suddenly became very cyanotic and immediately died. Autopsy showed the trachea and bronchi full of the feeding. It is assumed that either the tube had been passed into the trachea or that she had vomited and aspirated the feeding which caused her death.

It is regrettable that this patient died, presumably from the aspiration of a feeding; however, it is to be noted that she had successfully weathered a very severe degree of pulmonary hypoventilation. We feel confident that the reestablishment of satisfactory air exchange in this patient was directly attributable to the intermittent positive pressure breathing.

In conclusion, we believe that positive pressure respiration has definite value in dealing with respiratory paralysis in poliomyelitis, both in increasing the ease of movement of the patient and in the prevention and treatment of certain of the pulmonary complications which develop in the paralyzed patient. It is hoped that this preliminary clinical study will encourage similar efforts in other epidemics.

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PURPURIC MANIFESTATIONS OCCURRING IN MEASLES IN CHILDHOOD

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THE occurrence of an unusual complication in a disease as common as measles provides a stimulus for further inquiry into its frequency. Personal experiences with a child exhibiting purpuric manifestations following measles has prompted this review. This is not to be confused with the type of measles which is characterized by a hemorrhagic initial rash and usually terminates fatally.

CASE REPORT

A 6-year-old boy whose condition had been followed from birth and who gave no history of previous bleeding tendencies was seen with a fever of 103° F. and Koplik's spots in the buccal mucosa. Beyond injection of the conjunctivae, the physical examination did not reveal any abnormality at this time. He was given 4 c.c. of gamma globulin intramuscularly, and also aspirin for the fever. A typical measles rash appeared two days later. He was not unusually ill with measles and was not seen until a week after the first visit, at which time the rash was fading and he had a mild cough with nasal congestion.

Ten days after the onset of the disease he complained of bleeding from his mouth. He had had no fever for three days and had been up and about the house. At this time there were petechial hemorrhages on his legs and trunk. There were two small excrescences of the buccal mucous membrane opposite the last molar teeth which bled on pressure. The liver, spleen, and lymph nodes were not enlarged. The boy did not feel ill. The erythrocyte and leucocyte counts of the circulating blood were normal. The platelet count was 37,300 per cubic millimeter and the bleeding time was seventy minutes. Determination of the clot retraction time was not done.

Two days later he had severe epistaxis which was uncontrollable by the use of nasal packs, and he was hospitalized. The nasal hemorrhage temporarily stopped after insertion of an epinephrine pack. He was given 250 c.c. of whole blood by transfusion. He continued to bleed from the nose, and cauterization of the vessels of the nasal septum was done on two occasions. Blood in the amount of 250 c.c. was given six times at almost daily intervals. Petechiae continued to appear on the skin, tongue, and oral mucous membrane. There was no enlargement of the liver, spleen, or lymph nodes. The blood showed a moderate secondary anemia and leucocytosis with normal differential counts and continuously low platelet counts that ranged from 20,000 to 40,000 per cubic millimeter. The boy was dismissed from the hospital improved, on the fifteenth day after admission. There were no further hemorrhages of the skin or mucous membrane but his platelet count was still 37,500.

Two weeks after dismissal from the hospital the platelets numbered 90,000 and three months later they had risen to 140,000. There was no recurrence of bleeding and the erythrocyte, leucocyte, and differential counts were normal. The boy improved steadily and made a complete recovery in every way.

A review of the records from the files of the Mayo Clinic in the pediatric age group for the past thirty years revealed ten instances of purpura follow-

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ing measles. No case was considered in which the purpura did not develop within a month of the onset of the measles rash. Six patients showed the bleeding tendency within two weeks of the onset of the measles exanthem.

The patients were evenly distributed as to sex. The ages varied from 11 months to 8½ years. Two patients gave a history of repeated nosebleeds.

The bleeding was into the skin and mucous membranes in six cases and into the skin alone in four. Epistaxis was reported in one-half the cases. Hemorrhage from the bowel occurred twice, and from the urinary tract, once. Enlargement of the liver, spleen, and lymph nodes was recorded in two cases. Blood studies showed a mild to moderate degree of secondary anemia.

The number of blood platelets was reduced below 90,000 in four cases, with prolongation of the bleeding time beyond fifteen minutes. Clot retraction was delayed beyond two hours in three of the four cases in which the test was done. The diagnosis of thrombocytopenic purpura was made and splenectomy was carried out in three of the four cases. Splenectomy was deferred in the fourth case as the symptoms seemed milder than in the other cases.

Recovery of all but two patients took place. One of these was a 21-month-old female infant with a history of fever, petechial hemorrhages of the skin, and melena eight days after the onset of the measles rash; she died the day following admission to the hospital despite three blood transfusions. Necropsy disclosed a bleeding Meckel's diverticulum as well as hemorrhages throughout the bowel and stomach. The liver and spleen were normal in size, and the platelet count and the bleeding time were normal. Clot retractility was not recorded. A diagnosis of toxic purpura was made in this instance.

The second death occurred in the case of a 9-year-old boy one month after dismissal from the hospital. He had purpura involving his lower extremities. His platelets numbered 36,000 and the blood smear showed evidence of acute leucemia. One other patient had evidence of leucemia in the blood smears but he could not be followed up after his return home.

After elimination of the four patients with thrombocytopenic purpura and two with leucemia in whose course the occurrence of measles might be considered incidental, there remained four patients who could reasonably be considered to have had purpura following measles. All of these recovered except the infant with the Meckel's diverticulum and intestinal hemorrhages. No treatment was given to any of these patients except the transfusion of blood performed in the case of the child who died. In the other three patients the purpura was mild and lasted but a few days. It involved only the skin and not the mucous membranes. There was no enlargement of the liver, spleen, or lymph nodes reported, nor were the blood platelet counts or bleeding time abnormal. Estimations of clot retractility were not done in any of these patients. It would seem that in a case of uncomplicated measles, the appearance of purpura need not be a serious prognostic sign. As all but three of the previous ten cases were encountered prior to the advent of sulfonamide therapy, these drugs were not a factor in the production of the purpura. Though

amidopyrine has been incriminated in causing damage to the hemopoietic system as evidenced by purpura, there was no record of its use by any of the patients whose records were reviewed. It may be recalled that this drug was in vogue in the treatment of measles more than a decade ago.

A review of the literature on the subject of purpura following measles reveals a dearth of information in the standard textbooks of pediatrics or hematology. The most recent edition of Holt and McIntosh's textbook[1] mentions the occurrence of several instances in which thrombocytopenic purpura followed measles in the convalescent period and persisted for four to six weeks. The patient who has been reported on in detail in the first part of this paper appears to have had such a condition. In none of the other texts consulted was there any reference to this condition.

Fortune,[2] in 1904, reported on a 5-year-old girl in whom petechiae, epistaxis, and hematuria developed five days after the onset of the measles rash. There was enlargement of her spleen. She made a complete recovery. No blood studies were reported.

Nicholson[3] in 1917 mentioned a 17-year-old boy who made a complete recovery following a purpuric rash on his face and neck and who had cerebral symptoms on the fifth day after the onset of his measles rash. No blood findings were reported.

A year later, Lindsay[4] wrote of a 22-month-old girl whose rash became purpuric three days after the onset of measles without increase in the constitutional symptoms. Recovery occurred in two weeks. There was no information about the blood of this patient.

Kelly[5] in 1922 mentioned a 17-year-old boy who, on the seventeenth day of his measles, experienced the development of a purpuric rash on his body and a butterfly distribution of cutaneous hemorrhages over his cheeks and nose. Death followed soon after the petechiae appeared.

Laurent[6] in 1933 reported on an 8-month-old boy who had fever, diarrhea, and purpura of the face and extremities ten days after the subsidence of his measles rash. The leucocyte, erythrocyte, and platelet counts were within normal limits. Recovery followed treatment with antiscarlatinal serum and whole blood. The purpura was ascribed to damage to the capillary endothelium.

A year later Perlman[7] described a 4-year-old boy whose convalescence from measles was uneventful until a week after the appearance of the rash, when ecchymoses of the skin and mucous membranes, abdominal pains, hematuria, and a hematoma of the knee ensued. The platelet count was 90,000 but had increased at the time of dismissal. The bleeding time was thirty-seven minutes and the coagulation time two and one-half minutes. Estimation of retractility of the clot was not reported. Whole blood was given intramuscularly for four days. Perlman felt that purpura following measles was due to thrombocytopenia and found the platelet counts low in fifty cases of measles taken at random. He also noted that purpura occurred in other acute exanthemata and believed it to be allergic in nature.

Sarrouy[8] in 1934 remarked that purpura was rare following measles but was frequent after smallpox and scarlet fever. His patient was a boy aged 4½ years who had bleeding of the gums, nose, bowel, and kidney nine days after the onset of the measles rash. Petechial hemorrhages were also present in the skin. The platelet count was 8,800; the bleeding time was twenty minutes. There was no retractility of the clot. The blood picture returned to normal after ten days following two injections of whole blood from the parents, and the child recovered.

Miller[9] noted the rarity of purpura following measles and reviewed the literature to 1941. He collected reports of eight cases with cutaneous manifestations and seven with purpura of the mucous membrane and viscera. His patient was a 5-year-old boy whose bleeding from the nose, mouth, genitourinary tract, and skin began four days after the onset of his measles rash. He had a platelet count of 10,000 per cubic millimeter and his bleeding time was prolonged. Capillary fragility was increased. There was no retractility of the clot in twenty-four hours. Treatment with vitamin P, blood by transfusion, and liver extract resulted in complete recovery. The fact that vitamin P had been used in treating purpura following arsenical poisoning suggested its use in the condition under discussion. Miller felt that purpura in his patient was due to an allergic response following toxic damage to the capillary endothelium as well as to the thrombopoietic tissue of the bone marrow.

SUMMARY

Purpura as a complication of measles is not of common occurrence. Ten instances were found in a review of the pediatric case records of the Mayo Clinic for a period of thirty years, and one case is reported herein.

Purpura may afford evidence of an underlying blood dyscrasia. Of eleven reported patients in whom purpuric manifestations followed measles, four were found to have thrombocytopenic purpura and two, leucemia. The remaining five patients showed little or no increase in the size of the liver, spleen, or lymph nodes. Only one of these had a definite thrombocytopenia with prolongation of the bleeding time. There were two deaths in the eleven cases reported.

The outlook for the ultimate recovery of patients who exhibit purpuric manifestations following measles is good. However, one must be certain that such purpura is not an evidence of a blood dyscrasia or the accompaniment of a severe infection.

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URINARY LYSOZYME

I. Identification and Measurement

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THE presence of bacteriolytic agents in biological fluids has been known since the early days of bacteriology. One of these agents was named lysozyme in 1922 by Fleming,[1] who made an extensive study of its properties and activities. In 1940 Thompson[2] summarized work on many aspects of the substance. Lysozyme may be described as a basic protein or polypeptide, which is an enzyme capable of hydrolyzing a specific mucopolysaccharide found in some species of bacteria. The presence of lysozyme is conveniently demonstrated by its ability to clarify opaque suspensions of susceptible bacteria. The test organism most frequently used is the *Micrococcus lysodeikticus*.

Lysozyme has been said to be absent from normal urine.[1] It seemed reasonable to believe that since it is a normal plasma constituent of relatively low molecular weight (18,000-25,000) it might, under certain circumstances, appear in the urine. A preliminary search for a lytic agent for *M. lysodeikticus* in urine revealed that, whereas normal individuals excreted little or none, some patients with the nephrotic syndrome excreted it in considerable quantity.

IDENTITY OF URINARY LYTIC AGENT AND LYSOZYME

Since substances other than lysozyme can cause lysis of *M. lysodeikticus*,[3] a comparison of the properties of the urinary lytic agent and egg white lysozyme was undertaken to determine whether the two were identical.

Both agents were stable to heat in acid solution and were inactivated by heat in alkaline solution. Both were readily adsorbed onto bentonite; neither was eluted by washing with phosphate buffer but both were eluted by 5 per cent aqueous pyridine at pH 5.0. Both were soluble in two volumes of ethyl alcohol and were precipitated by five volumes of ethyl alcohol. Both were precipitated by picric acid, flavianic acid, and trichloracetic acid.

The lytic activity of dilute egg white lysozyme was inhibited by M/1,000 sodium dodecyl sulfate.[4] The lytic agent of urine specimens containing small quantities of protein was also readily inactivated by sodium dodecyl sulfate, but, when the protein content of urine was high, the inhibitory effect of sodium dodecyl sulfate on the lytic agent was suppressed unless the specimens were diluted considerably.

Egg white lysozyme acts with varying effectiveness on many air-borne bacteria. Ten morphologically distinct but otherwise unidentified bacteria were isolated from the laboratory air. A 0.1 per cent solution of egg white in 0.85 per cent sodium chloride caused lysis of varying degrees in seven of these, but had no effect on the other three. The urinary lytic agent caused lysis to approximately the same degrees of the seven lysozyme-susceptible bacteria, and failed

From the Alfred I. du Pont Institute of the Nemours Foundation.

to produce lysis of the resistant bacteria. A strain of *M. lysodeikticus*, which was induced to become partially resistant to egg white lysozyme, was found to be partially resistant also to the urinary lytic agent.

On the basis of the above similarities there can be little doubt that the urinary lytic agent is identical with the lysozyme of egg white.

One apparent difference between the two lytic agents was observed. The lysate resulting from the action of egg white on *M. lysodeikticus* was somewhat viscous. That produced by urine containing the lytic agent was nonviscous. Normal urine was shown to contain a substance which, although itself incapable of causing lysis of the test bacterium, was able, nonetheless, to reduce the viscosity of egg white lysate rapidly. The nature of the viscosity-reducing substance is not known, but preliminary investigations indicate that it is an enzyme, and since a highly purified preparation of desoxyribonuclease,* similarly reduces the viscosity of the egg white lysate, it may very well be that the urinary substance is desoxyribonuclease.

THE MEASUREMENT OF LYSOZYME

When lysozyme-containing solutions are added to suspensions of *M. lysodeikticus*, several associated reactions occur, and some of these have been used as a basis for determining the quantity of lysozyme present. For the measurement of lysozyme in urine, the viscosimetric method of Karl Meyer could not be used because of the effect of urine itself on the viscosity of the substrate. Likewise, a determination of the nonprotein nitrogen, phosphorus, or sugar released on lysozyme action was impractical since all these substances are, or may be, in urine in varying concentration. Agar-cup growth-inhibition tests were not satisfactory because of the small area of diffusion about the lysozyme cylinder. Microscopic examination of the sediment for absence of formed elements was too cumbersome.

The optical changes which accompany lysis of susceptible bacteria are readily visible, an opaque suspension of bacterial cells becoming almost water-clear. By testing the ability of serial dilutions of unknown lysozyme-containing materials to cause visible lysis of a standardized suspension of the test organism, an estimation of the quantity of lysozyme present may readily be made.[1] Other workers have shown that the completeness with which a constant amount of lysozyme induces visible clearing of a bacterial suspension depends on the time allowed for the reaction to take place, the temperature at which the test is performed, the pH and electrolyte content of the medium, the susceptibiltiy of the test organism to lysis, and the density of the suspension of the test organism. These factors have been taken into account in the method described below.

Time.—It has been found that lysis is complete after two hours' incubation, and that almost never has additional clearing of the bacterial suspension occurred after that time.

Temperature.—A temperature of 45° C. was selected for the test, since at that temperature lysozyme action is more rapid than at lower temperatures, bacterial growth is largely inhibited and urinary proteins are not coagulated.

*Obtained through the kindness of Dr. Maclyn McCarty of The Hospital of The Rockefeller Institute, New York.

pH.—The visible lysis of *M. lysodeikticus* is the result of two processes: the hydrolysis of the mucopolysaccharide of the bacterial cell wall and the solution of the cellular contents in the surrounding medium. The optimal pH for lysozyme action on its isolated substrate in vitro is about 3.5. At this low pH, however, lysozyme causes little or no visible clearing of a bacterial suspension. If lysozyme has been in contact with the test organism at pH 3.5 for sufficient time and the pH is then increased to 6 or higher, immediate clearing occurs. The absence of visible lysis at the low pH was attributed to insolubility of some cellular constituents at that pH. At a pH of 6.5 fairly rapid lysozyme action and complete clearing of the suspended cells occurs, and that pH has been found satisfactory for the test.

When a suspension of *M. lysodeikticus* is added to normal urine of neutral reaction a rapid increase in pH occurs. This is due to action of urease present in *M. lysodeikticus*, since a washed suspension of the organism added to a pure, neutral solution of urea causes a similar increase. Attempts to prevent an undesirable rise in pH by inhibiting urease activity without interfering with the test were unsuccessful. Stabilization of pH with M/30 phosphate buffer of pH 6.5 satisfactorily retards pH rise, as indicated in Table I.

TABLE I. EFFECT OF PHOSPHATE BUFFER ON pH AND LYSIS DURING LYSOZYME TEST*

	DILUENT: 0.85% NaCl		DILUENT: M/30 PHOSPHATE BUFFER	
PATIENTS	FINAL pH	LYSIS	FINAL pH	LYSIS
J. K.	8.2	++++	6.9	++++
L. E.	8.3	++++	7.0	++++
B. J.	8.2	+++	6.8	++++
J. S.	8.2	++	7.3	+++
E. L.	8.3	+++	7.0	+++
S. F.	8.3	++++	6.8	++++
F. S.	7.4	–	6.9	+
H. M.	8.3	–	6.9	+
H. I.	8.5	+	6.9	++
K. Z.	6.8	+	6.7	++
M. H.	7.9	–	6.8	–
M. C.	8.6	–	6.9	+

*Suspensions of *M. lysodeikticus* and dilutions of urine were made with 0.85 per cent NaCl solution or with M/30 phosphate buffer of pH 6.5 as indicated. Final dilution of urine was 1:4 in all tests, and the initial pH of all tubes was 6.5. pH determinations and readings for lysis were made after incubation of tubes in water bath at 45° C. for twenty-four hours. Minus sign (–), no visible lysis; pluses (+ to ++++), increasing degrees of lysis.

Electrolyte Content.—The optimal concentration of electrolyte for the action of lysozyme on the test organism is equivalent to approximately 0.5 per cent sodium chloride. Lysis is slow and incomplete in distilled water and is entirely inhibited by 8 per cent sodium chloride solution. Since the electrolytes in urine specimens vary widely in concentration, and since there is no convenient method either to determine their concentration in urine or to remove them from urine, the only practicable step in minimizing their effect is by the use of a solution of optimal salt concentration for the dilution of urine and for suspension of the test organisms. M/30 phosphate buffer has been used for these purposes because it is sufficiently concentrated to make up for the low electrolyte content of dilute urines but is not so concentrated that it interferes with lysozyme action in concentrated urines. Nevertheless, some lysozyme-containing urine specimens show lysis when diluted 1:4 or more in this solution, but fail to show lysis when diluted 1:2 or 1:1. The occasional failure of the more concentrated mixtures of

urine to produce lysis was attributed to high initial salt content. For this reason the highest proportion of urine to other ingredients of the test mixture employed in the test is 1:4. No urine specimen was encountered which failed to cause lysis in this concentration but caused it in greater dilution.

Test Organism.—The susceptibility of *M. lysodeikticus* to lysozyme is greater than that of any other known microorganism. A descendent of Fleming's original strain can be obtained from the American Type Culture Collection (No. 4698). A stock culture of this strain was kept at 4° C. on tryptose phosphate agar slants, and was used to inoculate other tryptose phosphate agar slants for the test. The slants for the test were incubated at 37° C. for forty to forty-eight hours before use. The organisms from slants incubated only twenty-four hours were somewhat less susceptible to lysozyme than were the older growths, and the bacterial yield was considerably less.

The strain of *M. lysodeikticus* used in these studies has been quite stable in its susceptibility to lysozyme. Two suspensions were compared, one of which derived from stock culture slants which had been kept at 4° C. for six months. The other had been kept in the lyophiled state for the same period, and was recovered shortly before use. The lysozyme susceptibility of suspensions of the two strains, determined in parallel with several urine specimens of varied lysozyme content, was identical. This stability is a highly important feature of the test, since on it depends the reproducibility of results. Unfortunately, there is no preparation of lysozyme which can serve as an absolute standard of lysozyme potency, since the content of natural lysozyme-containing materials is variable and to date experience with crystalline lysozyme is inadequate.

Feiner, Meyer, and Steinberg[6] investigated the characteristics of three strains of *M. lysodeikticus*. All the strains were thought to have derived from the original organism isolated by Fleming in 1922. One had been, for many years, in the laboratory of those workers, another was received from the American Type Culture Collection, and a third was received recently from Dr. Fleming. The three strains varied in certain respects, particularly in immunological characteristics. Within the limits of error of the serial-dilution method used, however, those workers could demonstrate no difference in sensitivity to lysozyme among the three strains.

Reading. There are two satisfactory ways in which the end-point of the test may be read. Visible inspection of a series of tubes in which progressive dilutions of the urine have acted on the test suspension shows a degree of dilution beyond which the urine causes no change in the suspension. The reciprocal of the greatest dilution causing a visible change is the arbitrary unitage of lysozyme contained in the unknown specimen. The photoelectric determination of end points has not been used because urine imparts color of variable intensity to the mixtures, interfering with turbidometric determinations at wave lengths in the blue and violet parts of the spectrum where turbidometric readings are best made.

Since the bacterial cell is killed and is no longer able to reduce methylene blue after lysozyme action, the end point of the test may be read by adding methylene blue to tubes containing progressive dilutions of urine and observing the greatest dilution of urine which interferes with the decoloration of the dye.

This method has the advantages of sharpening the end point somewhat and of being readily read, even when turbid fluids are assayed. Preliminary studies indicate that it may be used with good results for the assay of lipemic plasmas of nephrotic patients and other turbid biological fluids.

Other Factors.—Lysozyme is an exceedingly stable material which greatly facilitates the handling of urine specimens collected for assay. If desired, thymol may be added to inhibit bacterial growth since it does not interfere with the test. In most of the work reported here the specimens were stored without preservative in the refrigerator at approximately 4° C. These specimens were naturally contaminated with mixed bacterial species, but the bacteria appeared to have no recognizable effect on the lysozyme content of the specimens. Duplicate determinations of lysozyme content of fresh urine specimens and the same specimens to which no preservative was added but which had been kept in the refrigerator seven days revealed no loss or increase in lysozyme content. Sulfadiazine, penicillin, and streptomycin in urine or added to egg white did not interfere with the lytic effect of lysozyme, did not cause lysis of *M. lysodeikticus,* and did not interfere with methylene blue reduction. The existence of any substances in urine inhibitory to lysozyme has not been suspected.

TECHNIQUE OF URINARY LYSOZYME MEASUREMENT

The urine specimen to be tested is adjusted to pH 6.5 with 1N hydrochloric acid or sodium hydroxide, using bromthymol blue as an indicator, and is then centrifuged. The clear supernate is used to start serial dilutions, which are made in Pyrex agglutination tubes of 9 mm. internal diameter. A double row of tubes is placed in a rack, the number of tubes depending on the expected lysozyme content of the material to be tested. In each tube in the first row is placed 1.0 ml. of M/30 phosphate buffer, of pH 6.5,* then 1.0 ml. of urine is added to the first tube in this row. This is mixed thoroughly with the buffer by means of a pipette, and 0.5 ml. of the mixture is transferred to the empty tube immediately behind. 1.0 ml. of the remaining mixture in the first tube is then transferred to the second tube in the first row with a fresh pipette and is mixed with the buffer in that tube. 0.5 ml. of the mixture is transferred to the tube immediately behind, and, with a fresh pipette, 1.0 ml. of the mixture is transferred to the third tube in the front row. This procedure is followed until the series is completed. The tubes in the front row are discarded and the tubes in the second row, each containing 0.5 ml. of fluid, are used in the test.

The test organism, *M. lysodeikticus,* grown on a tryptose phosphate agar slant (2 per cent agar) at 37° C. for forty-eight hours, is washed off the slant with 5 ml. of M/30 phosphate buffer of pH 6.5 and thoroughly emulsified by blowing in and out of a 5 ml. pipette. This suspension is further diluted with buffer until it absorbs 50 ± 1 per cent of the transmitted light measured by a Coleman, Jr. photoelectric colorimeter at wave length 425, employing 10 mm. round cuvettes with distilled water as the reference standard. Suspensions should be made freshly from forty-eight-hour cultures. Suspensions that have stood in the laboratory more than three hours are unsatisfactory.

*1,000 ml. of M/30 phosphate buffer of pH 6.5 is prepared by adding 300 ml. of M/30 Na_2HPO_4 (4.734 Gm. of the anhydrous salt per liter of distilled water), to 700 c.c. M/30 KH_2PO_4 (4.536 Gm. of the anhydrous salt per liter of distilled water).

To each tube containing urine diluted in series is now added 0.5 ml. of the standardized suspension of *M. lysodeikticus*. Thus the final dilution of urine in the first tube is 1:4, in the second 1:8, in the third 1:16, etc. Two control tubes are prepared. One contains 0.5 ml. of bacterial suspension plus 0.5 ml. of phosphate buffer, and serves as a lysozyme-free control. Another tube contains 0.5 ml. of bacterial suspension plus 0.5 ml. of 0.1 per cent egg white in 0.85 per cent sodium chloride, and is used to demonstrate the lytic susceptibility of the suspension. The rack is then placed in a water bath at 45° C. for two hours, at which time readings are made. The reciprocal of the greatest dilution of urine to cause visible lysis is the number of units of lysozyme per milliliter of urine. Thus, if a urine specimen produces visible lysis at a dilution of 1:128 but shows no visible lysis at a dilution of 1:256, the urine has 128 units of lysozyme per milliliter.

When reading the test, conditions of lighting must be such that minor differences in turbidity can be readily distinguished. Suitable illumination is supplied by blue fluorescent light directed toward the tubes from below, the tubes themselves being viewed against a dark background.

If desired, the end point may be determined by an alternative procedure. After termination of the two-hour period of incubation, to each tube of the test is added 1 drop, 1:2,500 *alcoholic* methylene blue solution. The tubes are then gently agitated to distribute the dye, and the surface is overlaid by a layer one inch deep of clear mineral oil. The tubes are incubated in the water bath at 45° C. for an additional period of thirty minutes before reading. Tubes uniformly blue throughout are read as positive for lysis. Tubes in which the methylene blue is decolorized (except for a narrow layer of blue color immediately under the oil) are read as negative. The lysozyme content is the reciprocal of the greatest dilution of urine read as positive. The end point of the test when methylene blue is used agrees with that obtained by the observation of visible lysis within one serial dilution.

SUMMARY

1. The bacteriolytic agent present in urine which causes lysis of *M. lysodeikticus* is identical in properties with egg white lysozyme.

2. A technique has been described for the measurement of the lysozyme content of urine.

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URINARY LYSOZYME

II. Lysozymuria in Healthy Children and in Children With Miscellaneous Diseases (a Sex Difference)

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FLEMING reported[1] that normal urine did not contain lysozyme. He listed "urine containing much albumin and pus" among the biological materials in which he found lysozyme, but no reports of any systematic study of urinary lysozyme were found in the literature.

When we observed that lysozyme was present in elevated quantities in the urine of some, but not all children with the nephrotic syndrome, the question arose as to how frequently, and in what quantity, lysozyme might be excreted by normal children and by children with various other diseases; herewith are presented the results of a study of those aspects of the problem. In the next communication[2] lysozymuria in a group of nephrotic children will be considered.

MATERIAL AND METHODS

Single urine specimens were obtained from a group of 428 Philadelphia public school children, a group of sixty-two infants and preschool children at St. Vincent's Hospital for Women and Children, and a group of 105 school-age girls at the Catholic Home for Girls, Philadelphia. These children ranged in ages from less than one year to 18 years, and none of the children was suffering from any obvious disease process.

In order to determine the incidence of lysozymuria in children with various diseases, urine specimens were obtained from 144 patients on the pediatric wards of the Temple University Hospital and St. Christopher's Hospital, Philadelphia, from the Harriet Lane Home, Baltimore, and from the orthopedic wards of the Alfred I. du Pont Institute.

Single voided specimens were obtained from each of the children studied. Except for a few hours during transit to the laboratory, the specimens were kept refrigerated until the tests were run. No preservative was used.

Urinary lysozyme was determined by the method which has been described in detail in the first paper of this series.[3]

RESULTS

1. *Normal Children.*—Of 595 presumably normal Philadelphia children, 440 excreted less than 4 units of lysozyme per milliliter of urine (Table I). One hundred fifty-five children excreted between 4 and 32 units of lysozyme per milliliter of urine. No child in this group excreted more than 32 units, and on the basis of that finding we have tentatively accepted 32 units per milliliter as the upper limit of normal.

From the Alfred I. du Pont Institute of the Nemours Foundation.

TABLE I. URINARY LYSOZYME IN PHILADELPHIA CHILDREN

AGE GROUPS	LYSOZYME UNITS PER MILLILITER URINE					TOTAL NO. CHILDREN	CHILDREN WITH 4 TO 32 UNITS	
	0	4	8	16	32		NO.	% OF TOTAL
Male								
0-5	23	1	1	0	2	27	4	14.8
6-10	37	0	1	0	0	38	1	2.6
11-15	52	4	0	0	0	56	4	7.1
16-19	51	1	0	0	1	53	2	3.8
Unknown	8	1	0	0	1	10	2	20.0
All ages	171	7	2	0	4	184	13	7.1
Female								
0-5	23	6	8	2	1	40	17	42.5
6-10	103	17	13	2	1	136	33	24.2
11-15	63	15	5	5	1	89	26	29.2
16-19	60	11	28	13	2	114	54	47.4
Unknown	20	6	5	1	0	32	12	37.5
All ages	269	55	59	23	5	411	142	34.5

A difference was observed in the excretion of detectable (but normal) amounts of lysozyme by children of the two sexes. Of the males, 7.1 per cent excreted 4 or more units of lysozyme per milliliter of urine, whereas 34.5 per cent of the females excreted 4 or more units.

Although no extensive studies have been made to determine possible explanations for the sex differences in lysozyme excretion, two points have been investigated briefly. First, the question arose as to whether or not contamination of urinary specimens by vaginal secretions might account for the higher proportion of lysozyme-containing urines in girls. Two girls were selected for this study, both of whom excreted moderate quantities of lysozyme from time to time in their urine. A urine specimen, voided in the usual way, was obtained from each child, following which the vulva and anterior vagina were lavaged with 50 ml. of sterile saline solution. After cleansing of the vagina and vulva by this lavage, another urine sample was obtained. Lysozyme determinations were made of the initial and final urine samples and of the vaginal lavage material. In neither case was there detectable lysozyme in the material used for lavage nor was there a change in the lysozyme content of the urine before or after lavage. It is thus unlikely that the vaginal secretions were a source of the urinary lysozyme in girls.

In order to determine whether or not the sexual difference in lysozyme excretion might occur also in other species, urine specimens were collected from a group of male and female rabbits (Table II). Three out of sixteen male rabbits, or 19 per cent, excreted detectable lysozyme in their urine. Their specimens contained, respectively, 8, 32, and 8 units per milliliter. In contrast, 100 per cent of ten female rabbits excreted lysozyme, ranging from 8 to 512 units per milliliter. The proportion of male to female lysozyme excretors (1:5) was approximately the same in the rabbit and human populations, although in both sexes rabbits excreted lysozyme more frequently and in larger quantity than did human beings.

In order to determine whether or not a source of urinary lysozyme might be from ingested lysozyme-containing materials, a normal adult male who ordinarily

TABLE II. URINARY LYSOZYME OF RABBITS

MALE RABBITS		FEMALE RABBITS	
RABBIT	LYSOZYME UNITS/ML. URINE	RABBIT	LYSOZYME UNITS/ML. URINE
No. 51	0	No. 63	32
No. 52	0	No. 65	32
No. 53	0	No. 66	512
No. 56	0	No. 68	128
No. 61	8	No. 69	128
No. 62	0	No. 78	8
No. 75	0	No. 38	8
No. 73	0	No. 76	128
No. 27	32	No. 67	32
No. 37	8	No. 58	32
No. 70	0		
No. 12	0		
No. 77	0		
No. 15	0		
No. 99	0		
No. 80	0		

did not excrete detectable quantities of lysozyme in his urine, took by mouth on an empty stomach one pint of raw egg white containing approximately 100,000,000 units. Serial collections of naturally voided urine specimens were obtained over a period of forty-eight hours following this ingestion. Detectable quantities of lysozyme did not appear in his urine. It is apparent, therefore, that the ingestion of egg white does not cause the appearance of lysozyme in the urine of a normally alysozymuric individual.

2. *Children With Miscellaneous Diseases.*—Urine specimens were obtained from 144 children with diseases other than the nephrotic syndrome and pyelonephritis from the pediatric wards of the hospitals mentioned above. The diseases represented in these children consisted of the many acute and chronic conditions which may be encountered at any one time on pediatric wards of active hospitals. Since there was no tendency for lysozyme excretion in moderate quantities to be associated with any particular disease or group of diseases, no useful purpose would be served by listing each patient and his diagnosis.

Of the 144 children, only two excreted more than 32 units of lysozyme per milliliter of urine. One of these was a patient with typhoid fever. His urine contained 5.7 Gm. of protein per liter of urine and 256 units of lysozyme per milliliter of urine. The other was a premature infant who had pneumonia. His urine contained less than 70 mg. of protein per liter and 64 units of lysozyme per milliliter.

The occurrence of lysozymuria in the premature infant prompted an investigation of the frequency with which lysozyme might appear in the urine of premature infants. Specimens were obtained from ten such infants through the courtesy of Dr. Henry Barnett of the New York Hospital. None of these infants excreted detectable quantities of lysozyme in his urine.

There were 142 children out of a total of 144 whose lysozyme excretion did not exceed the upper limit of normal (32 units per milliliter) as established in the healthy Philadelphia children. Of 74 boys, 12.2 per cent and of 68 girls, 39.7 per cent excreted between 4 and 32 units of lysozyme per milliliter of urine

TABLE III. URINARY LYSOZYME IN DISEASES OTHER THAN NEPHROTIC SYNDROME*

HOSPITAL	LYSOZYME IN UNITS PER MILLILITER URINE					TOTAL NO. CHILDREN	CHILDREN WITH 4 TO 32 UNITS	
	0	4	8	16	32		NO.	% OF TOTAL
St. Christopher's Hospital and Temple University Hospital								
Male patients	36	2	0	1	1	40	4	10.0
Female patients	24	4	4	2	1	35	11	31.4
Harriet Lane Home								
Male patients	9	1	0	0	0	10	1	10.0
Female patients	7	3	1	0	1	12	5	41.7
Alfred I. du Pont Institute								
Male patients	20	2	1	1	0	24	4	16.7
Female patients	10	3	6	2	0	21	11	52.4
All Hospitals								
Male patients	65	5	1	2	1	74	9	12.2
Female patients	41	10	11	4	2	68	27	39.7
Both sexes	106	15	12	6	3	142	36	25.4

*Two patients with abnormal lysozymuria have been eliminated from this tabulation. One, a premature infant with pneumonia, excreted 64 units of lysozyme per milliliter and the other a 7-year-old boy with typhoid fever, excreted 256 units per milliliter.

(Table III), figures which do not deviate significantly from those of healthy children of the two sexes.

DISCUSSION

Small amounts of lysozyme were excreted by 7.1 per cent of the boys and 34.5 per cent of the girls in a group of 595 presumably normal Philadelphia children. The children studied were prepubertal and adolescent in age. The number of children in any of the age groups was too small to warrant drawing conclusions concerning a difference in the proportion of lysozyme excretors at any particular age as compared to any other.

The excretion of small amounts of lysozyme apparently constitutes a childhood sex difference which is maintained at least through the period of puberty. That the difference in lysozyme excretion between boys and girls is a real one is beyond question. If the boys and girls are divided into two classes each on the basis of the excretion of less than 4 units on one hand and the excretion of 4 or more units on the other, the results may be analyzed for significance according to Fisher's fourfold table. Chi square for these groups is found to be 50.3, which makes the probability exceedingly unlikely that the difference between the boys and the girls was due to a chance distribution of cases.

Unfortunately, the least quantity of lysozyme which we are able to detect in urine with the present technique is 4 units per milliliter. It would be interesting to know what the relative proportion of lysozyme excretors might be in the two sexes could lesser quantities of lysozyme be detected reliably. It is possible that all individuals excrete small amounts of lysozyme, and that the difference between girls and boys is quantitative.

The fact that the sex difference in lysozyme excretion in human beings was observed also in rabbits suggests the desirability of accumulating information about the phenomenon in other animal species in order to determine whether it may have a more general biological distribution.

Although the percentage of children in the group with miscellaneous diseases who excreted 4 or more units of lysozyme per milliliter of urine was practically the same as in the healthy Philadelphia children (26.0 per cent compared to 25.4 per cent, Table IV), the similarity has little meaning since the distribution of the sexes in the two groups was not the same. When the children are analyzed separately according to sex, it can be seen that the excretion of detectable amounts of lysozyme occurred somewhat more often in individuals of either sex in the ill children than in the normal children of the corresponding sex. The difference observed, in samples of the size involved, could readily arise as a result of chance alone (Males: chi square = 1.75; females, chi square = 0.68), and it is probable, therefore, that the excretion of lysozyme in patients with a variety of acute and chronic illnesses (excluding patients with the nephrotic syndrome, pyelonephritis, and two patients with abnormally high lysozymuria) was essentially the same as in healthy children.

TABLE IV. COMPARISON OF LYSOZYMURIA IN HEALTHY PHILADELPHIA CHILDREN AND IN CHILDREN WITH MISCELLANEOUS DISEASES

	LYSOZYME IN UNITS PER MILLILITER URINE				TOTAL NO. CHILDREN
	LESS THAN 4 UNITS		MORE THAN 4 UNITS		
	NO. CHILDREN	% OF TOTAL	NO. CHILDREN	% OF TOTAL	
Male					
Healthy Philadelphia children	171	92.9	13	7.1	184
Children with miscellaneous diseases	65	81.8	9	12.2	74
Female					
Healthy Philadelphia children	269	75.5	142	34.5	411
Children with miscellaneous diseases	41	60.3	27	39.7	68
Total					
Healthy Philadelphia children	440	74.0	155	26.0	495
Children with miscellaneous diseases	106	74.6	36	25.4	142

SUMMARY

1. Lysozyme was found in the urine of 26 per cent of 595 healthy infants and children. The quantity of lysozyme present in such urines did not exceed 32 units per milliliter.

2. Girls excreted lysozyme in their urine about five times as often as did boys. The increased frequency of lysozymuria in girls was not due to contamination of urine by vaginal secretions.

3. Female rabbits excreted lysozyme in their urine more frequently than did male rabbits.

4. A single ingestion of one pint of raw egg white did not lead to the appearance of lysozyme in the urine of a normally alysozymuric male over the subsequent forty-eight hours.

5. The urinary lysozyme excretion of 142 of 144 children with a variety of acute and chronic diseases (exclusive of the nephrotic syndrome and pyelonephritis) was not significantly different from that of the healthy children in incidence, in quantity, or in distribution according to sex. Only two of the 144 patients excreted abnormally large quantities of lysozyme. They were diagnosed typhoid fever and prematurity complicated by pneumonia, respectively.

ACKNOWLEDGMENTS

The authors are greatly indebted to the following organizations and individuals for specimens which were generously supplied for this investigation: The School Nursing Service of the Philadelphia Board of Education; Dr. Waldo E. Nelson and Dr. Mary Richardson of Temple University Hospital and St. Christopher's Hospital, Philadelphia; Dr. Francis Schwentker and Dr. Lewis Thomas of The Harriet Lane Home, Baltimore; Dr. Henry A. Barnett of New York Hospital; Sister Alice Delores of The Catholic Home for Girls, Philadelphia and St. Vincent's Hospital for Women and Children, Philadelphia.

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THE DEVELOPMENT OF THE AEROBIC BACTERIAL FLORA OF THE THROAT IN NEWBORN BABIES

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IN SPITE of the great amount of work which has been done, the significance of the various bacteria which may be present in the upper air passages is not yet fully clear. Certain organisms are obviously the cause of, and are found in the presence of an acute infection, as, for example, hemolytic streptococci in scarlet fever. Other bacteria, not necessarily in association with infection, are frequently recovered on chance culture in the process of being swallowed, expectorated, or destroyed. Their isolation on a single occasion and their absence a few hours later clearly mark their positions in the respiratory tract flora as transients which do not actually colonize but which to all intents and purposes behave as inert foreign particles. There are, however, still other organisms essentially nonpathogenic but constantly to be found in the upper air passages, usually in large numbers. They seem to be highly adapted to growth on the mucous membranes of the mouth and throat and make up what one may call the normal basic flora.

It seems evident that a precise definition of this basic normal flora is essential for a full understanding of the bacteriology of the upper air passages both in health and in disease. What constitutes the list of organisms which fall into this category? Is the basic flora common to all localities or are there variations at different times and in different places? Are these organisms always harmless or may they on occasion produce disease? How early in life do they appear and what is the nature and mechanism of their adaptation to growth in the upper air passages?

In an attempt to reduce this problem to the simplest terms we studied, some years ago, the development of the aerobic flora in the throats of newborn infants.[1] It was found, in brief, that the pharynx was sterile at birth, but as soon as the infant nursed a variety of bacteria appeared. The most constant and abundant were nonhemolytic streptococci of various sorts. A variety of other bacteria were also obtained, staphylococci, *Micrococcus tetragenus*, diphtheroids, etc., most of them obviously derived from the skin and nipples of the nursing mother. The common pathogens of the upper air passages such as hemolytic streptococci, pneumococci, meningococci, and others were conspicuously absent, doubtless because no clinical infection had as yet occurred. Neisseria were sometimes present early; colon bacilli were never found. Kneeland later confirmed these findings.[2] He noted the sterility of the upper air passages at birth, the prompt development of a flora in which nonhemolytic streptococci predominate, and the absence at first of pathogenic bacteria.

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METHODS

The opening at Stanford Hospital of a nursery for the newborn infant in which rigid isolation technique is observed offered an ideal chance to re-explore the development of the flora of the upper air passages under controlled conditions. In this nursery conditions of sterility are maintained which compare with those of a surgical operating room. The babies are isolated in small wards in which disinfection of room air is promoted by standard ultraviolet light technique. Two of the four rooms receive only filtered air. In order to lay lint and dust, all linen is treated with a cationic germicidal emulsion similar to that described by Schechmeister and Greenspan in 1947.[3] The babies' clothing is sterilized. The nurses invariably wear sterile gowns and masks, and after scrubbing thoroughly with green soap and water, rinse their hands for one minute in a 1:3,000 Zephiran solution. While in the nursery they wear cap, mask, and short-sleeved gown. Before going from one infant to another, the hands and arms are dipped in the Zephiran solution. No doctors enter the nurseries. When a baby is to leave the nursery to visit the mother or for examination, he is handed, wrapped in a blanket, to a nurse outside wearing cap, mask, and long-sleeved surgical gown. When the baby is returned the used blanket is discarded as the infant is passed through the swinging glass door into his nursery. Transportation to the mother is accomplished via a mobile cart containing six covered cribs.

Bottle-fed infants are fed sterile water twelve hours after birth and sterile formula twenty-four hours after birth. These babies visit their mothers once every twenty-four hours and on the third and subsequent days of life in the hospital are held by their mothers during one feeding daily. Except for the physical examination shortly after birth, removal once or twice a day to a glass-protected room for inspection by visitors, and the visits to the mothers, the bottle-fed infants do not leave their nursery until they are dismissed from the hospital. Most of the babies leave the hospital on the fifth day. Breast-fed babies are nursed by their mothers on a four-hour schedule beginning twenty-four hours after birth. The mothers wear masks during all feedings and visitors are excluded from their rooms.

Eleven newborn infants were the subjects of this study, by means of which we sought to answer several specific questions: (1) How long is the establishment of a bacterial flora in the upper air passages delayed by the aseptic technique used in the nursery? (2) Is the affinity of the mucous membranes of the throat for certain nonhemolytic streptococci so great that the organisms will become established even though they cannot be demonstrated in the ward? (3) What are the various categories of bacteria which sooner or later must appear in the throat even under the conditions of isolation described above? All cultures were taken in the doctors' examining room adjoining the nurseries. The babies were brought to the room in the manner described, and cultures were made immediately, using a sterile tongue blade, by passing a sterile cotton applicator back and forth over the posterior pharyngeal wall between the tonsillar fossae. Plating was done within ten minutes. Three blood agar plates and

one of MacConkey's agar were used for each culture. The original swab was rubbed thoroughly on the first plate. With a bent glass rod the inoculum was spread thoroughly over this plate and then transferred to the second and later to the third. Thus, three dilutions of the inoculum were obtained and one or more of the three plates always showed isolated discrete colonies. Moreover, by following this standardized method, a rough index of the total numbers of organisms on the swab was obtained. For example, in a normal adult or in an infant after the fourth day of life, the first agar plate would show nearly confluent growth, the second 1,000 to 4,000 colonies, and the third about 200 to 800 colonies. Such growth would be rated "4 plus," as recorded in the tables below. The MacConkey's agar plate was included to detect the presence of coliform organisms. It was inoculated by rubbing the swab back and forth across the middle of the plate and then streaking out the inoculum with a platinum loop. All cultures were incubated aerobically at 37° C. for approximately thirty-six hours.

Penicillin sensitivity tests were made with some organisms by inoculating a broth subculture on blood agar plates containing 0.05 unit, 0.1 unit, 0.2 unit, and 0.4 unit of penicillin per cubic centimeter.

All streptococci were subcultured in broth. Any organisms giving a diffuse growth were tested for bile solubility. In the series of infants receiving penicillin, cultures were made of all streptococci in methylene blue milk and 6.5 per cent sodium chloride broth to determine the presence of enterococci. The only beta hemolytic streptococci isolated (Case 4) were grouped by means of Lancefield sera.

Studies of the bacteria in the environment of the nurseries were done first with blood agar settling plates exposed for two and four hours, and second by means of a Duplex Electrostatic Air Sampler, D-E, described by Luckiesh and co-workers in 1946.[4] This sampler collects a very high percentage of air-borne bacteria from a measured amount of air directly on two blood agar plates so that numbers as well as individual organisms can be studied. Cultures from the nursery floors were made by wiping them with sterile, saline-soaked, cotton swabs.

RESULTS

Studies of Bacteria in the Environment.—

Studies of the air of the nurseries by blood agar settling plates showed very few bacteria. A single colony of gram-positive bacilli was found in a plate from one nursery. All other organisms found were *Staphylococcus albus* or *citreus*. The greatest number isolated in this way was thirty-five colonies, found in one plate exposed for four hours. The results are shown in Table I. Cultures from the floor showed four colonies of nonhemolytic streptococci from one nursery but none from the other three. Gram-positive bacilli and staphylococci were isolated in considerable numbers. The total number of colonies and the kinds of organisms found in ten cubic feet of air as measured with the Duplex Electrostatic Air Sampler are shown in Table II. There were two to three times as many colonies per ten cubic feet in three places outside the nurseries as within the

nurseries. The highest count was from Women's Medical Ward shortly after visiting hours. Nursery No. 1, in which no nurses were working during the twenty-minute test period, showed the lowest count. In the medical ward, laboratory, and at the nurses' station adjacent to the nurseries, the flora was more complex than that isolated within the nurseries. Only one colony of nonhemolytic streptococcus and two colonies of pneumococcus were found in the nurseries, whereas outside, five colonies of nonhemolytic streptococcus were isolated at the nurses' station, eight in the medical ward, and ten in the bacteriology laboratory. Unmasked persons came and went near the sampling machine during the twenty minutes required for the tests made outside the nurseries. Staphylococcus, chiefly albus, was the most frequent organism, and gram-positive rods ranked second. A very large, oval, gram-positive organism with a yellow, dry, cartwheel-like colony appeared in every culture and is referred to in Table II as "yellow fungus." Only two colonies of coliform organisms were found, one in nursery No. 2, and one in the medical ward. Hemolytic streptococci and *Neisseria sp.** were seen only in the cultures from the laboratory.

TABLE I. CULTURES OF NURSERY AIR MADE WITH SETTLING PLATES OF BLOOD AGAR

	NURSERY NO. 3*	NURSERY NO. 3*	NURSERY NO. 4	NURSERY NO. 4
Plates exposed for two hours				
Staph. albus	7	4	13	19
Total colonies	7	4	13	19
Plates exposed for four hours				
Staph. albus	2	1	31	25
Staph. citreus			3	2
Gram-positive bacilli			1	
Total colonies	2	1	35	27

*Nursery No. 3 was not in use.

TABLE II. TOTAL NUMBER OF COLONIES AND TYPES OF ORGANISMS FOUND IN TEN CUBIC FEET OF AIR MEASURED WITH DUPLEX ELECTROSTATIC AIR SAMPLER*

	NURSERY NO. 1	NURSERY NO. 2	NURSERY NO. 3	NURSERY NO. 4	NURSERY NURSES' STATION	WOMEN'S MEDICAL WARD	BACT. LAB.
Staphylococci	23	62	71	47	120	170	108
Gram-positive bacilli	5	5	0	6	15	48	14
Large gram-positive cocci	0	0	0	1	0	0	0
Coliform bacilli	1	0	0	0	0	1	0
"Yellow fungus"	3	5	5	6	23	30	10
Other fungi	0	0	0	0	2	0	6
Nonhemolytic streptococci	0	1	0	0	5	8	10
Neisseria sp.	0	0	0	0	0	0	3
Pneumococci	0	2	0	0	0	0	0
Hemolytic streptococci	0	0	0	0	0	0	3
Total colonies	32	75	76	60	165	257	154

*In Nursery No. 1 no nurses were working at the time the sampling was done. All staphylococci in the nurseries appeared to be *Staph. albus*, but in the other places tested several kinds of staphylococci were present. Several kinds of gram-positive bacilli were seen in the cultures from the medical ward and the laboratory.

*The term *Neisseria sp.* is used throughout this article to indicate gram-negative cocci which appear in cultures of the throat in a wide variety of colonial forms. *Neisseria catarrhalis* is the most well-known species.

Studies on the Normal Flora of Newborn Infants.—

Throat cultures were made on six babies at frequent intervals from a few hours after birth until the infant left the hospital. The results are shown in Table III. The first cultures taken one to three hours after birth were sterile in all six instances. A nearly pure flora of nonhemolytic streptococci was found in cultures taken from twenty-two to thirty-seven hours after birth in five cases. The predominant organism in the other baby, Case 3, was atypical culturally and morphologically, but it was also probably a nonhemolytic streptococcus. Because of a laboratory accident subcultures of it were lost so that definite identification was not possible. By seventy-four hours a more typical organism similar to that seen in the other infants had appeared and was vieing for predominance with the less typical coccus. *N. sp.*, so common in adult throats, appeared only twice in these six babies. In Case 1 it was transient in the seventy-eight-hour culture, and in Case 6 it was probably part of the resident flora, since it appeared in the last three cultures. In the total of fifty cultures made from the six infants, staphylococcus, chiefly albus, occasionally citreus, appeared in twenty-four cultures. Significant numbers comprising 1 per cent or more of the total growth after the flora was established appeared in ten cultures. These organisms, as shown by the air studies, were the most frequent in the environment. Their number waxed and waned from culture to culture, sometimes making up 20 per cent or more of the total growth and then falling off to an occasional colony in a culture made a few hours later. They were obviously transients and not permanent members of the normal flora. Gram-positive bacilli similar to those seen in the air cultures appeared as transients from time to time. The phenomenon of transients was well illustrated in the fourteen-hour and twenty-two-hour cultures of Case 6. At thirteen hours there was no growth of gram-positive rods; at fourteen hours there was moderately heavy, pure growth; and at sixteen hours, again no growth. A similar sequence of events occurred in the twenty-one, twenty-two, and twenty-five-hour cultures. Case 4 showed, in three consecutive cultures, a considerable number of hemolytic streptococci belonging to Lancefield's Group D. Large, gram-positive cocci, other than typical staphylococci, appeared as rare transients (in three of the six babies). Coliform organisms were found only once (Case 3), in spite of the MacConkey's plates used with all cultures to facilitate isolation of these organisms.

Studies of the total growth were of interest; they showed a gradual increase as time elapsed after the first establishment of the basic flora of nonhemolytic streptococci.

Case 1 was the only baby who was breast fed. He showed no striking differences from the other babies, either in respect to the time first growth appeared, complexity of flora, or total numbers of organisms.

Studies of the Flora of Newborn Infants Receiving Penicillin.—

The technique used in these experiments offered an unusual chance to study the influence of antibiotics on delaying colonization in the throat. Various amounts of procaine penicillin in aqueous suspension were given intramuscularly to five newborn infants a few hours after birth. Results of serial throat cultures are shown in Table IV.

TABLE III. RESULTS OF CULTURES

CASE 1. BREAST FED.

	HOURS AFTER BIRTH							
	1	10	22	30	46	55	78	103
Nonhemolytic streptococci	0	0	99+%	99+%	80%	99.9%	98%	99%
Neisseria sp.	0	0	0	0	0	0	1%	0
Staphylococci	0	0	rare	few	20%	rare	few	0.5%
Large gram-positive cocci	0	0	0	0	0	0	0	0.5%
Total growth	0	0	+	2+	3+	3+	4+	4+

CASE 2. BOTTLE FED

	HOURS AFTER BIRTH						
	1	10	22	38	45	69	93
Nonhemolytic streptococci	0	0	100%	99%	100%	98%	40%
Neisseria sp.	0	0	0	0	0	0	0
Staphylococci	0	0	1 col.	few	1 col.	0	60%
Large gram-positive cocci	0	0	0	0	0	2%	0
Total growth	0	0	+	2+	*	4+	4+

*Poor spread of the inoculum made estimation of total growth unreliable.

CASE 3. BOTTLE FED

	HOURS AFTER BIRTH							
	1	18	21	24	30	47	74	98
Nonhemolytic streptococci	0	0	0	0	0	0	98%	5%
Gram-positive cocci (possibly streptococci)	0	0	0	0	85%	95%	1%	75%
Neisseria sp.	0	0	0	0	0	0	0	0
Staphylococci	0	0	8 col.	12 col.	5%	5%	1%	20%
Coliform	0	0	0	0	10%	0	0	0
Total growth	0	0	8 col.	12 col.	+	3+	3+	3+

CASE 4. BOTTLE FED

	HOURS AFTER BIRTH						
	3	18	27	43	66	91	114
Nonhemolytic streptococci	0	0	65%	99%	40%	99+%	40%
Neisseria sp.	0	0	0	0	0	0	0
Staphylococci	0	0	35%	1%	10%	rare	20%
Large gram-positive cocci	0	0	0	0	0	0	0
Hemolytic Group D streptococci	0	0	0	0	50%	few	40%
Total growth	0	0	+	3+	3+	4+	3+

CASE 5. BOTTLE FED

	HOURS AFTER BIRTH						
	3	8	27	32	47	71	96
Nonhemolytic streptococci	0	0	100%	100%	100%	99+%	100%
Neisseria sp.	0	0	0	0	0	0	0
Staphylococci	0	0	0	0	0	0	0
Large gram-positive cocci	0	0	0	0	0	few	0
Small gram-negative bacilli	0	0	0	0	0	rare	0
Total growth	0	0	3+	3+	3+	3+	4+

CASE 6. BOTTLE FED

	HOURS AFTER BIRTH												
	1	13	14	16	17	18	21	22	25	26	37	61	85
Nonhemolytic streptococci	0	0	0	0	0	0	0	0	0	0	95%	99%	90%
Neisseria sp.	0	0	0	2 col.	0	0	0	0	0	0	5%	few	10%
Staphylococci	0	3 col.	0	0	0	2 col.	0	0	3 col.	0	0	0	0
Large gram-positive bacilli	0	0	100%	0	0	0	0	100%	0	0	0	0	0
Total growth	0	3 col.	3+	2 col.	0	2 col.	0	4+	3 col.	0	3+	4+	4+

TABLE IV. CULTURES IN BABIES RECEIVING PENICILLIN.

CASE A. BREAST FED*

150,000 units of procaine penicillin G in aqueous suspension were given I. M. at 4, 28, 58, and 82 hours after birth.

	HOURS AFTER BIRTH										
	4½	12	27	36	51	60½	75	87	99	108	123
Staphylococci	2	0	2	1	2	1	7	4	6	0	1,000
Total growth*	2	0	2	1	2	1	7	4	6	0	1,000

*The figures recorded in this table indicate the actual number of colonies grown.

CASE B. BREAST FED

150,000 units of procaine penicillin G in aqueous suspension were given at 4½ and 28½ hours after birth.

	HOURS AFTER BIRTH									
	3½	12½	27	36	51	60	75	84	99½	107
Nonhemolytic streptococci*	0	0	0	0	0	0	0	0	50%	99+%
Staphylococci	0	0	0	1 col.	1 col.	10 col.	8 col.	100%	50%	few
Total growth	0	0	0	1 col.	1 col.	10 col.	8 col.	1+	3+	4+

*Streptococci from the 99½ and 107-hour cultures were completely inhibited by 0.1. unit of penicillin per cubic centimeter in vitro.

CASE C. BOTTLE FED

150,000 units of procaine penicillin G in aqueous suspension were given I. M. 4½ hours after birth.

	HOURS AFTER BIRTH								
	4	12	28	31	52	60½	76	100	123
Nonhemolytic streptococci*	0	0	0	0	0	0	0	40%	50%
Staphylococci†	0	0	50 col.	0	3 col.	rare	0	60%	50%
Pneumococci‡	0	0	0	0	0	99+%	0	rare	0
Unidentified gram-negative bacilli	0	0	0	100%	0	0	0	0	0
Total growth	0	0	50 col.	1+	3 col.	2+	0	2+	3+

*The streptococci were resistant to 0.1 unit of pencillin per cubic centimeter but were inhibited by 0.2 unit per cubic centimeter.

†Staphylococci from the 100- and 123-hour cultures were resistant to 0.4 unit of penicillin per cubic centimeter in vitro.

‡The "pneumococci," though giving a diffuse growth in broth and dissolving readily in 10 per cent bile, did not show capsular swelling nor agglutination with any Pneumococcus-grouping serum.

CASE D. BREAST FED*

150,000 units of procaine penicillin G in aqueous suspension were given I. M. 3 hours after birth.

	HOURS AFTER BIRTH				
	2½	11½	26	35	50
Total growth	0	0	0	0	0

*The baby left the hospital on the third day.

CASE E. BREAST FED

150,000 units of procaine penicillin G in aqueous suspension were given I. M. 12 hours after birth.

	HOURS AFTER BIRTH					
	11½	43	58	67	83	107
Nonhemolytic streptococci*	0	0	90%	100%	100%	100%
Staphylococci	0	1 col.	10%	0	0	0
Total growth	0	1 col.	1+	3+	4+	4+

*Streptococci from the 58-, 67-, and 83-hour cultures were completely inhibited by 0.1 unit penicillin per cubic centimeter in vitro.

Case A received 150,000 units of the repository penicillin every twenty-four hours for four doses beginning four hours after birth. No nonhemolytic streptococci appeared in any of the eleven cultures. *Staph. albus* appeared in all but two cultures, but it never became definitely established, since very few colonies appeared in any save the last culture. Case B received two doses of 150,000 units of penicillin twenty-four hours apart, the first being given at four and one-half hours. Nonhemolytic streptococci became established between eighty-four and ninety-nine and one-half hours after birth. *Staph. albus* was the only other organism appearing in the ten cultures. Cases C, D, and E each received a single dose of 150,000 units of penicillin four and one-half, three, and twelve hours after birth, respectively. None developed a resident flora before fifty hours. Case D left the hospital after the fifty-hour culture with no aerobic organisms ever having appeared. Case C showed a moderate, nearly pure growth of pneumococci in the sixty and one-half-hour culture, a growth which proved to be transient, and finally developed a flora containing nonhemolytic streptococci and staphylococci between seventy-six and one-hundred hours. Case E developed a pure flora of nonhemolytic streptococci after the fifty-eight-hour culture, a light growth of a few staphylococci having appeared between forty-three and fifty-eight hours.

As mentioned above, the nonhemolytic streptococci were subcultured to special media for the identification of enterococci. None were found. The streptococci from Case C were the most resistant to the action of penicillin, being completely inhibited by 0.2 unit of penicillin per cubic centimeter but not by 0.1 unit per cubic centimeter. Streptococci from Cases B and E were completely inhibited by 0.1 unit of penicillin per cubic centimeter.

The only gram-negative organisms to appear in the series of babies receiving penicillin were found as transients in the thirty-one-hour culture of Case C. These organisms were short, slender rods which did not grow on the MacConkey's agar used in the original culture. On subculture they did grow on MacConkey's agar but did not ferment lactose and did not grow in typical, large, moist, coliform colonies. They were not studied further.

DISCUSSION

It is clear from the studies of the flora of the nursery air that the infants were exposed to relatively few bacteria. Moreover, nonhemolytic streptococci in the environment were excessively rare. In spite of this, the time of appearance of nonhemolytic streptococci in the throat in the first series of babies, who received no penicillin, was about the same as that reported in the earlier studies[1, 2] made in much less well-protected nurseries. *A very minute inoculum of nonhemolytic streptococci is evidently able to colonize* and probably persists throughout life as the basic aerobic flora. This affords striking proof of the amazingly close affinity of the mucous membranes for the nonhemolytic streptococcus. We have demonstrated[5] that these organisms appear to grow in close union with the mucous membrane, since intensive scrubbing and treatment with antiseptics failed to extirpate them.

As recently as 1945 other observers,[6] studying the flora of newborn infants, have interpreted staphylococci as being an integral part of the basic flora of the throat. It would appear from the present study that staphylococci, although very frequently isolated, come and go as transients, rarely appearing in large numbers and never persisting as an important part of the basic flora. The five infants in this study who were breast fed were continually exposed to a rich source of *Staphylococcus albus* from the mothers' nipples but did not develop a flora of staphylococci. Failure to understand the doctrine of transients and to recognize them as insignificant has led to great confusion in studies of respiratory tract bacteriology.

Other observers[7] have found numerous organisms to be present in the throat at birth. They noted that more bacteria were obtained after difficult deliveries than after normal births. The present observations, as indicated above, showed no organisms in cultures taken from one to twelve hours after birth, which suggests that contaminating organisms from the birth canal and delivery room are removed quickly.

According to previous work[8] *N. sp.* are well adapted to growth in the oral pharynx. In our experiments on adults[9] it has been noted that *N. sp.* are often present and often persist through many serial cultures but tend to wax and wane in number. There were, of course, no *N. sp.* demonstrated in the nurseries, but presumably these organisms, as well as nonhemolytic streptococci, are occasionally present, perhaps distributed in spite of the face masks of attendants. Since only one baby in this series showed *N. sp.* as an established part of the flora, it appears that a relatively heavy inoculum is necessary for them to colonize or that the infant's throat has some peculiar resistance to these organisms.

Penicillin delayed the establishment of the normal flora but did not appear to alter the kinds of organisms. Table IV shows that the antibiotic was highly efficient in preventing the colonization of nonhemolytic streptococci for several days. In Case C, for example, in which penicillin was given at four and one-half hours after birth, nonhemolytic streptococci did not appear until 100 hours. Furthermore, in most cases, aside from an occasional transient, there was no growth at all for some days. Case D, for example, left the hospital after five cultures over a fifty-hour period had not yielded a single colony of any sort. It is evident, therefore, that penicillin may be highly effective in preventing the colonization of bacteria, even when they have a great affinity for growth in the throat, and this principle may have a wide and useful application in the prophylaxis of diseases such as scarlet fever, pneumococcus pneumonia, and others. It is of great interest that the flora of these infants, unlike the flora of adults,[9] did not become a predominantly Gram-negative one and did not include any unusual penicillin-resistant bacteria. Establishment of colon bacilli as a part of the resident flora of the adult throat occurred in a previous study[9] only after more than twelve days of penicillin treatment. If the infants in this series could have been given penicillin and cultured for a longer period than five days, changes in the flora might have been evident.

SUMMARY

Six newborn infants kept in a modern nursery elaborately protected against potentially harmful bacteria developed, after approximately twenty-four hours of life, an aerobic throat flora which consisted of nonhemolytic streptococci. Once established, this flora persisted with great tenacity.

In only one of six infants did *N. sp.* appear as part of the resident flora during the first five days of life.

Staphylococci came and went in the throats of these infants but did not comprise a part of the true indigenous flora.

Penicillin, given in various dosage schedules beginning shortly after birth, delayed the establishment of nonhemolytic streptococci but did not alter the kinds of organisms recovered from the throat in five babies.

We are indebted to Dr. H. K. Faber, Dr. C. Havard, and other members of the Department of Pediatrics for assistance in making the cultures and for their courtesy in permitting us to make these studies in the nursery.

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INFECTIOUS LYMPHOCYTOSIS

A Report of an Epidemic in Children

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INFECTIOUS lymphocytosis is a benign process characterized principally by marked leucocytosis and absolute lymphocytosis. It was first described as a clinical entity by Smith[15] in 1941, who recognized that it had probably been previously reported as infectious mononucleosis occurring without clinical signs or symptoms. Thus it is entirely possible that Ryersbach and Lenert[12] earlier in 1941 were the first to report any sizable number of cases of infectious lymphocytosis. Their series included sixteen children from a rheumatic fever convalescent home. Over a six-month period these children had leucocytosis and lymphocytosis. Thelander and Shaw[17] reported a series of patients with infectious mononucleosis who had cerebral complications. They included two children with negative heterophile antibody tests and relative and absolute lymphocytosis. These may also be examples of infectious lymphocytosis.

In a later report Smith[16] described three cases of acute infectious lymphocytosis in children of the same family and a fourth case in a contact of the first group. He emphasized that infectious lymphocytosis was a definite clinical entity, was infectious, contagious, and had an incubation period of from twelve to twenty-one days. He added that the clinical signs and symptoms may be so mild as to escape attention, or there might be varying degrees of constitutional reaction, such as vomiting, fever, irritability, abdominal signs and symptoms, and occasional signs of involvement of the central nervous system. In his cases the heterophile antibody tests were negative. The leucocytosis and absolute lymphocytosis were due to an increased number of small lymphocytes. Lymph node biopsies in two cases were similar. The nodes had "degeneration of the lymph follicles and a striking proliferation of the reticulo-endothelium of the sinuses."[16]

Duncan[3] reported a patient with pronounced abdominal signs and symptoms and with evidence of possible involvement of the nervous system during the first week of the disease. Beloff and Gang[1] reported three cases from a children's camp in Connecticut. Two of these patients apparently had poliomyelitis and the third had clinical manifestations of poliomyelitis with marked leucocytosis and lymphocytosis as is seen in acute infectious lymphocytosis.

Finucaine and Philips[5] reported twenty-one patients from a sanatorium whose ages varied from 18 months to 5½ years. In no case were there any symptoms at the onset, and the leucocytosis was found in every instance by routine blood counts. The duration of the leucocytosis in these patients varied from two and one-half to seven weeks. They believed that this picture was caused by an infectious agent, efforts at isolation of which were fruitless.

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Duncan reported two cases in young adults but in these patients the extent of the lymphocytosis was less and its duration shorter than in children. A morbilliform rash was present in one case. This had not been previously reported. However, Yuskis[15] reported a young adult male who had a maculopapular rash during his clinical course.

The largest series of cases of this type is that of Peterman and co-workers,[11] who observed a mild epidemic in twenty-eight patients. Most of the patients were from the same children's home. Sixteen of their twenty-eight patients had diarrhea during the course of the disease. The total leucocyte counts ranged from 18,900 to 147,000 per cubic millimeter and the lymphocyte counts varied from 64 to 94 per cent of the total. The lymphocytes were described as being definitely mature, and small to medium in size.

Birge and Hill[2] have emphasized the possibility of confusing this condition with leucemia and report such a problem which arose in their experience. Lorenz, Hardy, and Alt[8] reported the disease in brothers of 4 and 6 years of age. Both had hyperplastic bone marrow, but the lymphocyte differential in the bone marrow was within normal limits. It is of specific interest that the bone marrow lymphocytes in the two cases were 24 and 23 per cent, respectively. Meyer[10] also reported two cases in children who had symptoms of upper respiratory infection. One of these patients had a palpable spleen and both had moderate lymphadenopathy. The bone marrow in one had 91 per cent lymphocytes and the other 55 per cent lymphocytes. Meyer considered a small "overripe" lymphocyte as pathognomonic of infectious lymphocytosis and stressed the absence of anemia and thrombocytopenia as distinguishing it from leucemia.

The disease has been reported by MacInnis[9] in Canada, Steigman[14] in England, Santos[13] from Uruguay, Gsell[6] from Switzerland, and Klemola and Hamarinen[7] from Finland.

Our study regarding this type of leucocyte response in children was initiated when a 29-month-old infant from the Sarah Fisher Home for Children was admitted to Providence Hospital because of a fracture of the tibia. In addition, he had an acute upper respiratory infection and minimal roentgenegraphic evidence of bronchopneumonia. This child had an initial leucocyte count of 48,000 per cubic millimeter with 88 per cent lymphocytes. The leucocyte count rose to 70,400 per cubic millimeter with 89 per cent lymphocytes before regressing to normal.

Because of the peculiar character of the differential and the very high levels of the total leucocyte count, we decided to survey a number of children at the Sarah Fisher Home for Children.

In the Home the children are housed in resident groups of ten to fifteen children. Our survey included the balance of the children in the resident group from which our patient came, the inmediately adjacent resident group, and two to four children from each of the other six resident cottages. These latter children were selected at random. Forty-nine children from the total population of 106 were examined.

In addition to the complete blood count and smear examination, the history and physical examinations were recorded. Sedimentation rates were done to ascertain the presence of active infection; cephalin-cholesterol flocculation tests were done because of a possible association with endemic infectious hepatitis; heterophile antibody tests were done to rule out infectious mononucleosis; and nose and throat cultures were made to determine any influence of the bacterial flora.

In those children in whom abnormal counts were found, we did total leucocyte and differential counts at weekly intervals and roentgenograms of the chest as clinically indicated. The children in this series ranged in age from 18 months to 6 years, but because of the peculiar age distribution of the institution, all but three were in the 2- and 3-year range.

After our initial series of leucocyte counts was complete it became apparent that the forty-nine children examined could be placed into one of three groups. This grouping was determined by the height of the total leucocyte count and by numerical alterations in either or both of the lymphocyte and eosinophile counts.

CLASSIFICATION OF CHILDREN (FORTY-NINE CASES)

Group 1 (17 cases): Total leucocyte count over 15,000 per cubic millimeter with a differential of over 70 per cent lymphocytes and/or eosinophiles of over 3 per cent.

A. Those in whom a complete cycle of lymphocytosis probably occurred (5 cases).
B. Those in a subsiding phase of lymphocytosis (9 cases).
C. Those with a chronic or persistent phase of lymphocytosis (3 cases).

Group 2 (19 cases): A total leucocyte count of less than 15,000 but with abnormal lymphocyte or eosinophile percentages.

Group 3 (13 cases—control group): Hematologic values within normal range.

According to this division, in *Group 1* are included seventeen patients who had total leucocyte counts of over 15,000 per cubic millimeter and lymphocyte counts greater than 70 per cent or eosinophile counts over 3 per cent. This group was further subdivided. Subgroup A included five patients in whom we felt that a more or less complete cycle of the disease was represented in the study; the nine patients of subgroup B are those in whom we felt that the lymphocytosis was in a subsiding phase at the time of the beginning of this study; and subgroup C consisted of three patients with what we believe to be a chronic or slowly regressing phase of lymphocytosis. In *Group 2* are included nineteen children who had total leucocyte counts less than 15,000 per cubic millimeter but with elevation of either or both of the lymphocyte or eosinophile count. In *Group 3* are included those thirteen children in whom the hematologic values were within normal range.

Clinical Findings.—Nasopharyngeal and respiratory tract infections were found in many patients in all groups. These are all included under the heading of respiratory infection and are not further differentiated. No examples of other disease forms, such as encephalitis, were noted.

In *Group 1, A* there was clinical evidence of a respiratory infection with or without pharyngitis and cervical lymphadenopathy at some time during the

course in all of the five patients represented in this group. Chest roentgenograms were taken of all five. In one there was atelectasis of the right middle lobe, in three there were evidences of bronchopneumonia, and the remaining one was normal. Of the three with bronchopneumonia, one was apparently active at the time of the highest lymphocyte count but in the other two the examination was negative at the time of the highest lymphocyte count. The one sedimentation rate done in this group was within normal limits.

Of the nine patients in *Group 1, B* there were eight with evidence of pharyngitis or cervical lymphadenopathy at some time during the course of the disease. In no instance did the respiratory infection seem to have any particular bearing on the height of the lymphocyte count. Of the nine patients there were seven in whom roentgenograms of the chest were made. In five of these there was evidence of bronchopneumonia which was demonstrated to clear in four and to apparently persist in one. In two instances the roentgenograms were negative. In this group of nine patients there were seven in whom sedimentation rates were determined. The fall varied from 8 to 38 mm. in one hour (Westergren) and were respectively 8 mm., 11 mm., 18 mm., 21 mm., 25 mm., 35 mm., and 38 mm. Using an upper limit of 20 mm. per hour as a normal, there were four of the seven values which were elevated and three which were within normal limits.

Of the three patients in *Group 1, C,* all had evidence of upper respiratory infection at some time during the course of the disease. In one of these a roentgenogram of the chest showed evidence of bronchopneumonia. Sedimentation rates were done in all three and proved to be normal in two (8 mm. and 12 mm.) and elevated in one (27 mm.). Here again the clinical and radiologic evidences of respiratory infection did not seem to be closely associated with alterations in the total hematologic picture. The heterophile antibody and cephalin-cholesterol flocculation tests were consistently negative.

In the nineteen cases in *Group 2* there were eleven patients in whom there was no history of recent acute illness nor any abnormal physical findings. In the other eight there was a history of rhinitis in one and pharyngitis in three. In the same patients there were enlarged cervical lymph nodes in four, physical evidences of pharyngitis in one, of rhinitis in two with reddening of the gums in two and patchy ulcerations of the buccal mucosa and of the tongue in one. The sedimentation rate was determined in seven of these children and the results were as follows: 32 mm., 25 mm., 22 mm., 16 mm., 9 mm., 8 mm., and 5 mm., respectively. Thus three values were elevated and four were within normal limits. The cephalin-cholesterol and heterophile antibodies in six children proved to be negative.

In the thirteen cases in *Group 3* there were six with evidences of a respiratory tract infection. This included a history of rhinitis in one and pharyngitis in two, physical evidences of cervical or other lymphadenopathy in four, enlarged tonsils in one, and evidence of acute rhinitis in one. In this group the sedimentation rate was determined in three individuals. These values were respectively 20 mm., 7 mm., and 5 mm. The cephalin-cholesterol and heterophile antibody tests done in four instances proved to be negative.

In these patients the clinical picture, roentgenographic findings, and evidences of active infection as judged by sedimentation rate values did not seem to correspond closely with the hematologic picture. Only one observation seems of importance; the children with the altered hematologic picture did seem to have slightly more prolonged and persistent respiratory infections. The persistently negative heterophile antibody and cephalin-cholesterol tests make us discard any thought of association between infectious lymphocytosis and either infectious mononucleosis or infectious hepatitis.

Bacteriologic Study.—Nose and throat cultures were performed on twenty-two of our patients. The results of these cultures are summarized in Table I.

TABLE I. BACTERIOLOGIC FINDINGS (TWENTY-TWO CASES)

	NOSE				THROAT			
	NO.	STAPHYLOCOCCUS	DIPHTHEROIDS	STREPTOCOCCUS	STREPTOCOCCUS	PNEUMOCOCCUS	HEMOPHILUS INFLUENZAE	NEISSERIA CATARRHALIS
Group 1								
A	1	1				1		1
B	7	3	4		7	3	2	1
C	3	3			3	3		
Group 2	7	4	1	2	7	6	1	1
Group 3	4	3	1		4	3	1	

These findings do not seem particularly significant and represent essentially normal cultural results. We were unable to identify *Listerella monocytogenes* in any instance.

HEMATOLOGIC COURSE

While there is no specific change in the total leucocyte count, the differential percentages of lymphocytes or eosinophiles, or the relative percentage of large lymphocytes in the smear, there are certain general trends which are of interest.

The course may be said to consist of an acute or ascending phase, a subsiding or descending phase, and a chronic or variable phase.

During the acute phase the total leucocyte count reaches a peak of 45,000 to 100,000 per cubic millimeter in from two to three weeks. In the subsiding phase the total leucocyte count varies from 18,000 to 60,000 and finally diminishes to approximately normal levels. This phase covers a period of two to three weeks. During the chronic phase the total leucocyte count may vary from 8,000 to 16,000 per cubic millimeter and fluctuates between this range from week to week. In our series this phase lasted from seven to twelve weeks.

In the differential count the lymphocyte percentage increases to high levels prior to the peak of the total leucocyte count and may vary from 70 to 94 per cent of the total. These high levels of the lymphocyte percentage persist through the subsiding phase and for one to three weeks in the chronic phase, following which the percentage begins to regress to approximately normal levels. Elevations above 70 per cent may persist for as long as twelve weeks.

The relative numbers of large and small lymphocytes during these periods have been studied, and in general large lymphocytes increase and reach their highest percentage at the time of the greatest total leucocyte response. The percentage of large lymphocytes usually falls at about the time of the fall in the total leucocyte count, following which the percentage of large lymphocytes increases quite markedly and is maintained at high levels, usually over 50 per cent, for periods up to twelve weeks.

The eosinophile count follows a peculiar course. During the height of the leucocyte response the eosinophile count is low or absent. At, just preceding, or just following the fall of the total leucocyte count to normal, the eosinophile count tends to rise. This rise may vary from 5 to 20 per cent and after a period of four to six weeks usually returns to essentially normal levels of under 3 per cent.

This trend which we describe for the total leucocytes count, the lymphocyte and eosinophile percentages, and the large lymphocyte response is of a non-diagnostic character, and it is only after a survey of a number of cases that such a tendency can be noted. At no time can the phase of the leucocyte response be used as a diagnostic means to determine the stage of the disease.

From our studies we are not convinced that the small, mature "over-ripe" lymphocyte is pathognomonic of infectious lymphocytosis. These are small lymphocytes with deeply staining hyperchromatic nuclei and with a scant amount of cytoplasm which is fairly deeply basophilic. There were several instances where the cells could be classified as meso- and macrolymphocytes and in these instances it was not uncommon for the nuclei to have a slight left shift. There was never enough alteration in these lymphocytes to suggest the immature cells found in leucemia. Another interesting finding was the appearance of eosinophilia with fall in the total leucocyte count as previously noted.[5] In no instance was either anemia or thrombocytopenia noted.

BONE MARROW EXAMINATIONS

Bone marrow examinations were done on four cases and in all the lymphocyte percentage was above normal. In one case the lymphocytes constituted 65.4 per cent of the nucleated cells and were small and mature in type. At this time the peripheral white blood count was 30,900 per cubic millimeter with 87 per cent lymphocytes. A second examination done twenty-three days later revealed 14.4 per cent of the nucleated cells to be lymphocytes, and at this time the peripheral white blood count was 13,900 per cubic millimeter with 52 per cent lymphocytes.

In a second case the lymphocytes comprised 67.8 per cent of the nucleated cells in the bone marrow and again were mostly small and mature. At this time the peripheral white blood count was 39,800 per cubic millimeter with 74 per cent lymphocytes. A second examination done twenty-three days later revealed only 11.8 per cent of the nucleated cells to be lymphocytes, and at this time the peripheral white blood count was 8,000 per cubic millimeter with 47 per cent lymphocytes.

In the third case the lymphocytes comprised 84.8 per cent of the nucleated bone marrow cells at a time when the peripheral white blood count was 70,400 per cubic millimeter with 89 per cent lymphocytes. The cells again were mostly small and mature. A second examination done fifteen days later revealed 83.8 per cent of the nucleated cells to be mature lymphocytes at a time when the white blood count was 8,400 per cubic millimeter with 62 per cent lymphocytes.

In the fourth case only one bone marrow examination was done. Lymphocytes, mostly of the small and mature variety, comprised 80.6 per cent of the nucleated cells. At this time the peripheral leucocyte count was 63,200 per cubic millimeter with 91 per cent lymphocytes.

THERAPEUTIC TRIALS

Three patients were treated with sulfadiazine, two with penicillin, and one with both. The latter patient was changed from sulfadiazine to penicillin because of a drug rash. The sulfadiazine had no effect on the clinical course as far as could be determined. Penicillin was used on the two patients with buccal ulcerations and did seem to speed the clinical recovery of these patients although the hematologic picture did not appear to be affected. The patient who received both drugs in succession appeared to benefit somewhat. Certainly, these patients are too few to draw any definite conclusion, but comparing those cases so treated with those not treated, it would appear probable that sulfadiazine and penicillin are not of specific value. Any clinical benefit probably was due to the effect of the drugs on secondary invaders.

DIFFERENTIAL DIAGNOSIS

Infectious lymphocytosis may be confused with other diseases characterized by leucocytosis and lymphocytosis, the most important of which are infectious mononucleosis and lymphatic leucemia.

Infectious mononucleosis is usually quite easily distinguished by the lymphadenopathy, especially of the cervical nodes, the lower white count (over 20,000 is unusual in mononucleosis), the atypical lymphocytes, and, finally, a positive heterophile antibody test.

In lymphatic leucemia the lymphadenopathy is definite, the spleen may be enlarged, and the blood and bone marrow smears reveal immature lymphocytes. Further, the child is more ill, often manifesting spiking fever, anemia, thrombocytopenia, bleeding tendencies, and finally death.

Infectious lymphocytosis is a benign disease, the diagnosis of which can at most be suggested clinically. The total leucocyte count and careful morphologic study are the only dependable diagnostic criteria. In our experience this should be thought of when young children manifest a rather persistent rhinitis and low-grade fever and have a paucity of other signs or symptoms. Other clinical manifestations reported by others may include vomiting, diarrhea, irritability, abdominal signs and symptoms, central nervous system signs and symptoms, and transient dermatitis.

We believe that this disease is probably communicable but were unable to gauge the incubation period.

CONCLUSIONS

1. The literature pertaining to infectious lymphocytosis is reviewed and a series of new cases occurring in mild epidemic form in small children is reported.

2. From a study of our patients we are not inclined to attribute any specific clinical picture to this disease. It is apparently not associated specifically with either respiratory infections, or hepatitis, but probably does occur in epidemic form.

3. Hematologically, the disease is characterized by an absolute leucocytosis and lymphocytosis of varying degrees which may persist for from four to seven weeks in the acute and from seven to twelve weeks in the subsiding and late phases. The lymphocyte morphology is not pathognomonic although large-sized mature cells tend to predominate in the phase of greatest leucocytosis and again in the phase immediately following recovery as indicated by a return to normal of the total leucocyte level. Eosinophilia is frequently found in the recovery phase.

4. In the bone marrow there is a high percentage of lymphocytes of normal mature morphology thus distinguishing infectious lymphocytosis from infectious mononucleosis and lymphatic leucemia.

5. The disease is apparently benign, self-limited, and sulfadiazine and/or penicillin in our patients had no beneficial effect.

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THE TREATMENT OF ACUTE LEUCEMIAS OF CHILDHOOD WITH FOLIC ACID ANTAGONISTS

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CHILDREN with acute leucemia, who previously lived only a few weeks, have been experiencing remissions lasting from a few months to a year or more in response to treatment with folic acid antagonists, notably Aminopterin (4-amino-pteroylglutamic acid) and A-Methopterin (4-amino-N^{10}-methylpteroylglutamic acid). These drugs have produced hematologic or symptomatic reversals of the leucemic picture in twenty of a group of twenty-four children presented in this study. Unfortunately, the reversal has not been permanent, and death from the disease eventually occurs.

The identification and synthesis of folic acid and the antagonists have been described elsewhere. The use of the antagonists in the treatment of leucemia was reported by Farber and associates,[1] who treated a group of sixteen children, ten of whom improved. In a later paper, [2] Farber reported improvement in somewhat over 50 per cent of sixty patients. Dameshek[3] reported an improvement in 34 per cent of a group of twenty-six patients. Other clinics have reported varying degrees of success.[4, 5]

The patients studied here were admitted to the hospital for diagnosis and initial treatment. Because of the inconsistency of the peripheral blood studies and the clinical findings, the diagnosis of leucemia was based upon characteristic changes in the bone marrow. Confirmatory evidence was obtained from lymph node biopsies, roentgenograms of the skeleton, and peripheral blood studies. When the diagnosis was established, intramuscular injection of 1.0 mg. of Aminopterin daily was begun. The drug was discontinued when toxic lesions occurred or a hematologic depression appeared. After an interval of observation, treatment was resumed, 1.0 mg. being given intramuscularly every second day. If this was well tolerated and the peripheral counts remained stabilized, the patient was discharged to be followed in the Leukemia Clinic. Visits to the clinic were made three times weekly. The routine laboratory work consisted of a leucocyte count on each visit, an erythrocyte count, hemoglobin determination, and differential count once weekly unless indicated more often. Aminopterin was given on each clinic visit according to an arbitrary schedule generally depending upon the leucocyte count (a count of over 6,000 per cubic millimeter, 1.0 mg.; 2,000 to 6,000 per cubic millimeter, 0.5 mg.; and under 2,000 per cubic millimeter, none).

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Transfusions were given routinely to all patients when toxic signs appeared. They were also employed whenever the erythrocyte count fell to less than 1.5 million per cubic millimeter, sufficient blood being administered to raise the count to about 3.0 million per cubic millimeter. The patients were admitted to the hospital for transfusions.

In addition to the original bone marrow examination another was done during the recovery phase. Thereafter monthly examinations were made in the clinic. The sites of aspiration were alternated between the sternum and the iliac crests. The too frequent use of any one site led to failure to obtain a representative sample, presumably as the result of hemorrhage and fibrosis in the area of aspiration. When a high degree of leucemic infiltration was again found, and when clinical signs of leucemia returned, intensive treatment was repeated. Such subsequent attempts to bring the leucemic process under control usually did not meet with the success encountered in the original treatment. The use of a different antagonist (A-Methopterin) occasionally appeared to produce a greater response than did the Aminopterin used in the original plan of therapy.

Roentgen examination of the skeleton was obtained in almost every instance upon the initial admission and was repeated during the course of the illness. Skeletal lesions in initial roentgenograms were demonstrated in thirteen of the twenty-four children. Three children of nine with no demonstrable initial skeletal changes developed lesions later during the course of the disease. Four types of lesions were found: osteolysis, radiolucent transverse bands, osteosclerosis, and subperiosteal new bone formation. Adequate descriptions of these lesions have appeared previously in the literature.[6, 7]

The toxic lesions observed in these patients were limited to mucosal ulcerations of the mouth (Fig. 1) accompanied by some degree of fever. The lesions were erythematous patches with an ulcerated necrotic center which ultimately healed with the formation of a heavy crust. Only an occasional lesion became hemorrhagic. The ulcers were seldom painful although they were annoying, particularly in the healing stages. Attempts to hasten the healing process by the administration of crude liver extracts and folic acid were not successful. The most effective treatment consisted of the administration of sulfadiazene by mouth and the topical application of an aqueous solution of gentian violet. At autopsy, one patient was found to have an hemorrhagic lesion not definitely ulcerated and limited to one small area of small intestine.

All of the patients followed a similar hematologic course. The initial response was one of depression of the bone marrow, with reduction of all elements, normal and abnormal. The nucleated cell count of the marrow regularly fell to 400,000 to 500,000 per cubic millimeter, the normal for the method used being 1.0 to 1.2 million per cubic millimeter. The peripheral blood showed anemia and leucopenia. This phase was concurrent with the initial intensive therapy, and was one of the most critical phases in the course of treatment. The megakaryocytes and platelets were markedly reduced and bleeding tendencies occurred. With the discontinuance of the antagonist, the

cellularity of the marrow increased, with normal cells returning in greater numbers. The most normal marrow was found four to six weeks after therapy was instituted. In several patients the abnormal cells in the marrow dropped to less than 1 per cent of the total, and peripheral blood studies were entirely within normal limits. In spite of continued therapy, however, the number of abnormal cells in the marrow gradually increased. Appearance of abnormal cells in the peripheral blood was delayed, often not occurring until more than 75 per cent of the marrow cells were abnormal.

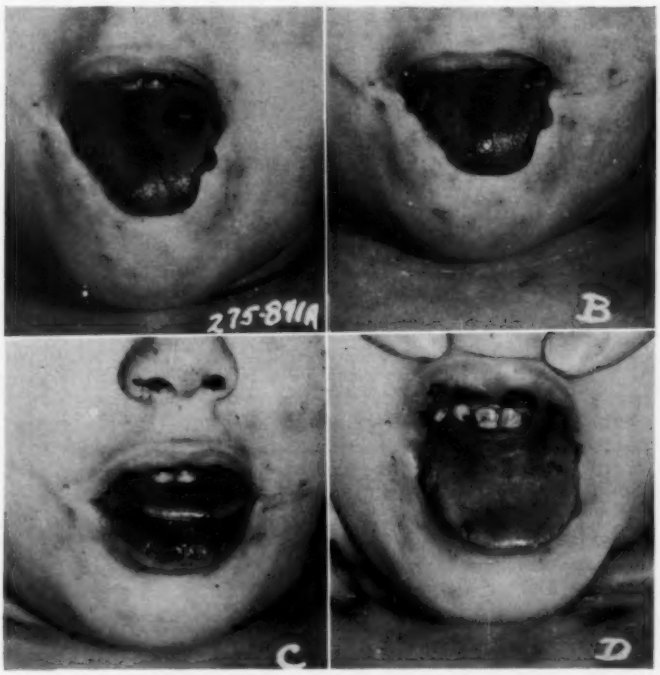

Fig. 1.—Toxic ulcerations of tongue and lips secondary to Aminopterin therapy.

In a few patients a second and fatal period of hematologic depression occurred after long-continued therapy. The peripheral blood showed a progressive anemia, leucopenia, and thrombocytopenia, relieved only temporarily by transfusions and withdrawal of the antagonist. The terminal course of these patients was that of an aplastic anemia. At autopsy it was possible to demonstrate severe hypoplasia of the marrow, and frequently little or no evidence of leucemia was present.

Although all of the patients showed a similar hematologic and symptomatic response, the degree of the response varied. Symptomatic relief occurred in some cases with only slight hematologic improvement. According to the varia-

TABLE I.

PATIENT	AGE	SEX	DURATION BEFORE TREATMENT	DURATION WITH TREATMENT	TYPE OF LEUCEMIA	RESPONSE*	BONE MARROW RESPONSE† (%)	AUTOPSY FINDINGS
K.R.	3 yr.	M	3 weeks	10 days	Acute	—	—	Leucemic infiltration, hemorrhage
C.B.	2 yr.	M	6 weeks	9 days	Acute	—	—	Leucemic infiltration, hemorrhage
G.O.	2 yr.	M	4 weeks	6 days	Acute	—	—	No autopsy
R.S.	3 yr.	M	12 weeks	48 weeks	Acute	H&S	14.6	Leucemic infiltration
S.K.	4 yr.	M	4 weeks	43 weeks	Acute	H&S	14.8	No autopsy
P.S.	8 yr.	F	13 weeks	12 weeks	Acute	H&S	39.6	No autopsy
R.K.	13 yr.	M	8 weeks	12 weeks	Acute	H&S	12.8	Hemorrhage, reticulum cell sarcoma
F.C.	4 yr.	M	4 weeks	29 weeks	Acute	H&S	15.2	
D.P.	2 yr.	M	4 weeks	17 weeks	Acute	H&S	36.2	No autopsy
L.T.	4 yr.	F	4 weeks(L)	12 weeks	Acute	H&S	11.8	Living
G.V.	3 yr.	M	5 weeks	20 weeks	Acute	H&S	21.4	No autopsy
H.W.	3 yr.	M	6 weeks	?	Acute	S	92.4	Unknown
S.B.	7 yr.	M	9 weeks	6 weeks	Acute	S	84.2	No autopsy
M.M.	3 yr.	F	3 weeks	31 weeks	Acute	H&S	4.0	No evidence of leucemia
C.H.	2 yr.	F	6 weeks	39 weeks	Acute	H&S	0.6	No autopsy
R.S.	19 mo.	M	3 weeks	32 weeks	Acute	H&S	6.2	Leucemic infiltration, hemorrhage
D.C.	8 mo.	M	2 weeks	12 weeks	Acute	H&S	1.0	Leucemic infiltration, hemorrhage
D.B.	3 yr.	M	8 weeks	24 weeks	Acute	H&S	6.8	No evidence of leucemia
T.K.	2 yr.	M	2 weeks	21 weeks	Acute	H&S	3.6	No evidence of leucemia
D.W.	5 yr.	F	6 weeks	34 weeks	Acute	H&S	7.4	Leucemic infiltration, hemorrhage
J.B.	4 yr.	M	2 weeks(L)	31 weeks	Acute	H&S	4.8	Living
J.S.	6 yr.	M	8 weeks(L)	20 weeks	Acute	H&S	9.4	Living
R.S.	4 yr.	F	4 weeks	8 weeks	Monocytic	?S	70.0	No evidence of leucemia
C.M.	2 yr.	F	3 weeks	17 weeks	Primitive	?S	88.2	No autopsy

*H, hematologic; S, symptomatic.
†Lowest percentage of blast cells found in the bone marrow during the patient's course.

tions in response, the patients could be divided into three groups. (See Table I.) The first group suffered a severe initial bone marrow depression and experienced hemorrhagic phenomena which contributed to their death early in the course of treatment. The second group had only moderate hematologic response but were markedly improved symptomatically. The number of abnormal cells in the marrow did not fall below 10 per cent of the total. The third group showed a decrease of abnormal cells in the marrow to less than 10 per cent, and, in two of the patients, to less than 1 per cent. The children in this group improved symptomatically to the point that they appeared to be completely well. None of the children exhibited an hematologic response without symptomatic relief. The following histories exemplify these variations:

CASE 1. K. R., a 2-year-old white boy, was admitted to Babies' and Children's Hospital of Cleveland April 29, 1948. His complaints were anorexia, irritability, malaise, easy bruising, and progressive weakness. Severe abdominal pain was experienced just prior to admission. Admission examination revealed fever, ecchymoses, petechiae, generalized adenopathy, and hepatosplenomegaly.

Laboratory studies showed: erythrocytes 3,180,000 per cubic millimeter, hemoglobin 7.0 Gm. per 100 milliliters, leucocytes 18,450 per cubic millimeter, with a differential count of granulocytes 1 per cent, lymphocytes 32 per cent, blasts 67 per cent. The platelets were reduced in number. The sternal marrow contained 99 per cent blast cells, 0.6 per cent erythroid cells, and 0.4 per cent myeloid cells.

Aminopterin was given 1.0 mg. intramuscularly daily. On the fifth day the erythrocytes fell to 1,800,000 per cubic millimeter, the leucocytes to 3,450 per cubic millimeter, with 11 per cent granulocytes and 23 per cent blast cells. On the eighth day the patient suddenly became lethargic, edematous, and dyspneic. A shower of petechiae was noted. The erythrocyte count was 970,000 per cubic millimeter and the leucocytes 2,500 per cubic millimeter with 10 per cent blast cells. In spite of the administration of oxygen and transfusions, the patient became worse and died on the tenth hospital day.

At autopsy a leucosis of the myocardium, lungs, liver, spleen, kidneys, pancreas, and bone marrow was found. Petechial hemorrhages were scattered throughout the tissues. The brain showed diffuse edema and multiple petechial hemorrhages in the brain substance.

CASE 2. M. M., a 3-year-old white female, was admitted to Babies' and Children's Hospital of Cleveland, June 25, 1948. For three weeks she had experienced progressive fever, malaise, and anorexia. Leg pain was noted on one occasion. A progressive pallor had also been noted. Admission physical examination revealed marked pallor, slight hepatosplenomegaly, generalized nontender lymph adenopathy, and absence of petechiae or ecchymoses.

Laboratory studies revealed: erythrocytes 1,920,000 per cubic millimeter, hemoglobin 5.0 Gm. per 100 milliliters, leucocytes 3,300 per cubic millimeter. The differential report was: granulocytes 3 per cent, lymphocytes 95 per cent, monocytes 1 per cent, and eosinophiles 1 per cent. The platelets were reduced in number. The bleeding and clotting times were slightly prolonged. The sternal marrow contained 98.8 per cent blast cells. Roentgenograms of the long bones demonstrated moderate osteoporosis with submetaphyseal rarefaction in the distal portions of both femurs.

Aminopterin, 1.0 mg., and crude liver extract, 2.0 U.S.P. units, were given daily for nine days. By this time the erythrocyte count was 820,000 per cubic

millimeter and the leucocyte count 500 per cubic millimeter. Several small transfusions were administered, after which the erythrocyte count was 2,040,000 per cubic millimeter and the leucocyte count 2,000 per cubic millimeter. The differential count was 54 per cent granulocytes and 46 per cent lymphocytes. The sternal marrow was re-examined on the twentieth hospital day and found to contain 4.0 per cent abnormal cells, few of which had nucleoli. The liver, spleen, and lymph nodes were no longer palpable. She was discharged on the twenty-first hospital day, to be followed in the clinic.

For five weeks the patient was asymptomatic. The peripheral blood studies remained within normal limits. Aminopterin was discontinued, and for the next five weeks she appeared healthy and happy. Subsequently she developed an upper respiratory infection, and a sternal marrow examination at this time demonstrated the presence of 72.4 per cent blast cells. Therapy with Aminopterin was resumed, but the patient continued to do poorly. On Oct. 9, 1948, she was readmitted for intensive therapy, improved markedly, and was again discharged after a 14-day stay in the hospital. In the ensuing months she had several episodes of toxic mouth lesions and required an increasing number of transfusions. Her course was progressively downhill and she expired Jan. 24, 1949. A bone marrow sample shortly before death revealed marked hypoplasia.

Multiple hemorrhages, recent hemorrhage into the mucosa of the jejunum, and fibrosis of the bone marrow were noted at autopsy.

CASE 3. S. K., a 4-year-old white boy, was admitted to Babies' and Children's Hospital of Cleveland June 28, 1948. He had experienced repeated traumatic "black and blue" marks for a period of eight weeks. For one month prior to admission he exhibited spontaneous ecchymoses and petechiae. Epistaxis was noted on several occasions. Admission examination revealed ecchymoses, petechiae, moderate pallor, generalized nontender lymph adenopathy, and slight hepatosplenomegaly.

Laboratory studies revealed: erythrocytes 3,840,000 per cubic millimeter, hemoglobin 8.5 Gm. per 100 milliliters, and leucocytes 43,900 per cubic millimeter, with a differential count of: granulocytes 5.0 per cent, lymphocytes 85 per cent, blasts 5.0 per cent, and normocytes 2.0 per cent. The platelets were markedly reduced in number. The bleeding and clotting times were slightly prolonged. The sternal marrow contained 96.8 per cent blasts.

Treatment with 1.0 mg. Aminopterin daily was given for seven days. At this time a severe episode of epistaxis occurred and Aminopterin was discontinued. A small blood transfusion was given and for the next seven days he received daily injections of crude liver extract. Blast cells disappeared from the peripheral blood and the leucocyte count ranged between 3,250 and 4,200 per cubic millimeter. A second sternal marrow examination revealed 14.0 per cent blast cells. Another small blood transfusion was administered and he was discharged on the seventeenth hospital day to be followed in the clinic.

He was seen three times weekly from July, 1948, to March, 1949. His appearance and activities appeared normal in all respects. The erythrocyte and leucocyte counts remained essentially within normal limits. After three months the marrow contained 78.8 per cent blast cells and after six months 98.2 per cent. There were no petechiae, ecchymoses, or hepatosplenomegaly.

In March, 1949, the parents withdrew the patient from the clinic and he received no further treatment. Five weeks later he was rushed to another hospital in extremis and expired the same day.

Two additional children, one with monocytic and one with a very primitive cell leucemia, were also treated. The latter patient showed some symptomatic

relief although there was no hematologic improvement. The patient with monocytic leucemia showed a marked diminution in the number of abnormal cells but no return of normal cells. Little symptomatic relief was afforded. The history was as follows:

CASE 4. R. S., a 4-year-old white girl, was admitted to Babies' and Children's Hospital of Cleveland, Sept. 13, 1948. For three months she had experienced progressive pallor, listlessness, and anorexia; for six weeks, easy bruising, fever, epigastric pain, and urinary frequency. One episode of hematemesis had been present. Admission examination revealed a chronically ill patient with pallor, ecchymoses, petechiae, generalized nontender lymphadenopathy, and hepatomegaly but no splenomegaly.

Laboratory studies showed: erythrocytes 1,410,000 per cubic millimeter, hemoglobin 3.9 Gm. per 100 milliliters, leucocytes 3,050 per cubic millimeter, with a differential count of: granulocytes 32 per cent, lymphocytes 37 per cent, monocytes 20 per cent, and blasts 11 per cent. Platelets were reduced. Bleeding and clotting times were prolonged. The sternal marrow contained 68 per cent blast cells which were oxidase positive and showed definite pseudopodia. Roentgenograms of the skeleton revealed no evidence of bone destruction or periosteal reaction.

Aminopterin was given in 1.0 mg. doses daily for nine days when a stomatitis indicated withdrawal. The peripheral blood studies and the bone marrow pictures remained essentially the same. Slight clinical improvement was noted and the patient was discharged after a three-week hospital stay. One week later she experienced hematuria, became very restless, and was readmitted to the hospital.

The examination was essentially the same as on the previous admission. The erythrocyte count was 1,450,000 per cubic millimeter and the leucocyte count, 3,500 per cubic millimeter. The urine was grossly bloody.

Aminopterin was given in 1.0 mg. doses daily for the next twenty-six days, along with 20 mg. of folic acid. She was given repeated small transfusions of whole blood. In spite of these, the erythrocyte count and hemoglobin remained low. Her condition became progressively worse and she died on the thirty-fifth hospital day after several bouts of severe hematemesis.

Autopsy examination revealed complete fibrosis of the bone marrow and myeloid metaplasia in the adrenals. No leucemic infiltration of the tissues was found. Multiple hemorrhages were found in the lungs, kidneys, and gastrointestinal tract.

A child with a malignant melanosarcoma and extensive metastases was also treated with Aminopterin. No alteration of the disease occurred as evidenced by the clinical course, roentgenographic findings, or autopsy examination.

Infection was a frequent complication in the course of these patients. Purulent otitis media and bronchitis were the most frequent. The results of treatment were discouraging, for the infections often failed to respond to any medication. Others appeared to respond and be completely healed, only to recur when medication was discontinued. Undoubtedly infection contributed to the death of several patients. While none of the antibiotics were found to be completely satisfactory, penicillin was the most effective.

Hemorrhage, likewise, presented problems of management. Petechiae and ecchymoses were the most common, although oral hemorrhage and epistaxis

were frequent. The bleeding was associated with a thrombocytopenia, and did not occur unless thrombocytopenia was present. The use of protamine sulfate or toluidine blue in doses of 2.0 to 3.5 mg. per kilogram of body weight failed to influence the bleeding and was considered to be evidence that hyperheparinemia did not contribute to the hemorrhagic tendency. The prothrombin levels remained normal until the terminal phases. It was difficult to determine whether the thrombocytopenia was the result of leucemic involvement of the marrow or the result of depression of platelet production by the antagonist. Regulation of the antagonist dosage was more effective in controlling hemorrhage than blood transfusions, which had only a temporary beneficial effect.

Three children who had attained hematologic and symptomatic remissions were placed on daily oral doses of 20 to 30 mg. of folic acid. The marrow, peripheral blood, and the clinical course were unaltered after periods of three to four weeks, indicating that the occurrence of relapse was not accelerated by the administration of folic acid in this dosage.

DISCUSSION

The use of folic acid antagonists has appreciably altered the course of leucemia in children. It has prolonged the life of many patients, affording them additional months of comfortable and frequently normal life. The ultimate outcome has not been influenced.

The most marked response occurred in that group of leucemias not readily definable morphologically. The criteria established for the identification of normal cells could not be satisfied by the abnormal cells found in the marrow or peripheral blood of these patients. The blast cell was large with a large nucleus and three to five nucleoli. The immature cell was the same size but had no nucleoli and the nucleus characteristically had an irregular outline. The mature cell was smaller with a dense, irregular nucleus. The entire series was oxidase-negative and studies with the supravital stain (Janus green and neutral red) did not reveal characteristics of mitochondria, vacuoles, or nuclear structure, which allowed the cells to be classified as typical of any of the recognized leucocyte groups. The cells involved presumably stemmed from an undifferentiated primitive cell. For these reasons, this leucemia has been termed "acute leucemia of childhood."

The cells of the patient with monocytic leucemia were oxidase-positive and were recognizable as monocytes in the peripheral blood. The patient with the very primitive cell leucemia showed oxidase-negative cells in the marrow which occurred as tumorlike syncytia containing three to eight nuclei.

The variation of the individual cases in response to the antagonists cannot be explained. It is difficult to determine whether the three patients who died in the first few days of treatment experienced any response. At autopsy the leucemia process did not appear altered; however, the initial depression, as manifested by findings in the peripheral blood, did occur. The greatest number of those patients who did respond eventually succumbed to a relapse of the leucemia. In these relapses the value of the antagonists diminished to the joint where they were no longer effective.

Five of the patients who experienced good remissions and were treated over a long period of time were found at autopsy to have scant, if any, evidence of leucemia. These patients all died in a manner suggesting aplastic anemia rather than leucemia, and at autopsy the bone marrows were fibrotic and essentially acellular. This suggests that while the leucemia could be controlled, a dose of antagonist sufficient to effect control was also sufficient to prevent normal hematopoiesis.

The mechanism of action of the folic acid antagonists cannot be defined with certainty. There is no doubt that a folic acid deficiency can be induced by their use, both in animals[8] and in bacteria. It appears probable that this could well be the sole mechanism of action. The effectiveness in controlling certain cases of leucemia can be explained by presuming that the more rapidly metabolizing malignant cells of leucemia are more susceptible to the development of a folic acid deficiency than are normal cells. Bethell has demonstrated[9] that immature leucocytes contain much more folic acid than normal leucocytes, which could be interpreted to mean that the folic acid requirement of the immature cells is greater than that of normal cells.

The failure of acute monocytic leucemia of children and acute lymphatic leucemia in adults to respond to antagonist therapy[10] is explained by presuming that while the cells in these cases are immature and have a more rapid metabolism, the difference between them and normal cells is not sufficient to allow significant alteration of the leucemic state without simultaneously causing serious interference with normal hematopoiesis.

The fact that the administration of folic acid to three of our patients did not cause rapid relapse after remission had been induced with antagonist therapy does not prove that a folic acid deficiency did not exist. It is reasonable to believe that antagonist treatment can cause disturbance in an enzyme system involving folic acid which could not be reversed immediately by supplying folic acid. It has been demonstrated in animals[8] that the effect of Aminopterin is overcome by folic acid only within a very marrow range, above which reversal does not occur.

An alternate explanation is that Aminopterin has a specific effect on cell growth unassociated with production of folic acid deficiency. It is the opinion of the authors that there is no good evidence for this view.

Thus, Aminopterin can interfere with a basic biochemical function of cell growth. Failure to maintain remission in patients with leucemia may be evidence that the primary biochemical defect in leucemia does not reside in the folic acid system. Thus, while the leucemic process can be controlled for varying periods of time, normal hematopoiesis is eventually disturbed to a point incompatible with life.

Although the folic acid antagonists do not allow satisfactory control of acute leucemia, they are more effective than other forms of treatment. While life can be prolonged for only a few to several months, symptomatic improvement is such that during much of this time the children are happy and apparently healthy and can lead essentially normal lives.

SUMMARY

1. Twenty-four children with acute leucemia were treated with the folic acid antagonists Aminopterin and A-Methopterin. Hematologic or symptomatic improvement, or both, occurred in twenty.

2. A dosage regimen is described.

3. Roentgen changes of the skeleton were present in thirteen children on the initial examination. Three children developed skeletal lesions during treatment. Four types of lesions were observed.

4. At autopsy, evidence of leucemia was sometimes minimal or absent. Severe hypoplasia of the marrow was encountered.

5. Infection and hemorrhages were frequent complications in these cases.

6. The mechanism of action of the antagonists is through production of a folic acid deficiency, although the action cannot be readily reversed by administration of folic acid.

7. Toxicity was manifested by ulcerative lesions of the oral mucous membranes.

8. While the antagonists did not constitute a satisfactory form of therapy for leucemia, they were more effective than other forms of treatment.

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HYALURONIDASE

Further Evaluation in Pediatrics

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ONE of the newer products that is demonstrating its value in many fields is hyaluronidase,* first reported as a "spreading factor,"[1, 2] with additional work[3-6] now indicating that it is a mucolytic enzyme which acts on and depolymerizes hyaluronic acid.

Hyaluronic acid[7] is a mucopolysaccharide acid which seems to bind water in interstitial spaces and also holds cells together in a jellylike matrix. It[8] has been shown to form an integral part of the basement membrane in various organs such as the kidney and thyroid. It[7, 9] has been found in synovial fluid, vitreous body, Wharton's jelly, ovarian follicular fluid, nucleus pulposus, papillary layer of the skin, perilobular stroma of the breast, stroma of the mucous membrane of the nasal cavity and trachea, and in a number of mesenchymal tumors of both humans and animals. Hyaluronic acid is a gel which is present in the ground substance of connective tissue and acts as a barrier to tissue diffusion, but hyaluronidase reduces its viscosity and facilitates fluid diffusion.

Hyaluronidase[7] has been found in many strains of bacteria such as staphylococci, streptococci, pneumococci, and *Clostridium welchii;* also in leech extracts, bee, snake, and spider venoms, spermatozoa, and mammalian testis.

Hyaluronidase content may be calculated by the following methods:[7, 10, 11]

1. By weight in micrograms.

2. By its diffusing activity in the skin. This can be done with India ink, such as blue dye T1824, which is nontoxic and available in a sterilized isotonic solution. Humphrey's method is followed, using guinea pigs. The minimum diffusion dose is the least amount of enzyme which will produce a 20 per cent increase of the mean area over the mean area of the control.

3. By mucin clot prevention. Ordinarily, hyaluronic acid in acid solution coprecipitates with protein in a typical fibrous mucin clot. After incubation with hyaluronidase, the quantity of the clot is reduced and the character of the precipitate changes from fibrous to flocculent until finally the solution remains clear. This measures the destruction by the enzyme of the power of a substrate protein complex to form a typical mucin clot on the addition of acetic acid.

4. By viscosimetry. This method measures the ability of hyaluronidase to decrease the viscosity of a standard solution of hyaluronic acid. One unit is defined as the amount of hyaluronidase required to reduce the viscosity 50 per cent in 30 minutes.

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*Hyaluronidase (Alidase) was supplied through the courtesy of Dr. Irwin C. Winter, Director of Clinical Research of G. D. Searle Co., Chicago, Ill.

5. By turbidimetry. This method is based on the observation that pure hyaluronidase at pH 4.2 gives a fairly stable colloidal suspension with dilute serum, whereas depolymerized hyaluronidase remains clear. One turbidity reducing unit is the amount of enzyme that reduces the turbidity caused by 0.2 mg. of hyaluronic acid to that caused by 0.1 mg.

Recently the work on hyaluronidase was thoroughly reviewed[7, 12] from the physiological and chemical standpoint, and several workers[10, 13-15] verified the fact that this enzyme greatly increased the rate of fluid absorption. In these reports[13-16] all agreed that there was no thermal response nor any accentuation of pre-existing infection. In most of these studies,[13, 14] temperature, pulse, blood pressure, and blood count were unaffected. In a more recent report,[15] urines and PSP tests also revealed no adverse effect.

With the increasing interest in hyaluronidase and the possibility of greater usage, it was felt that further studies relative to its safety were in order. In a previous paper,[10] it was shown in studies on six individuals that no abnormalities were detected in kidney, liver, and blood studies. In these cases, 0.02 mg. (0.2 c.c. of 100 μg per cubic centimeter) was given to each individual. In an attempt to test the effect of a larger dose, similar studies were done on two children using 1 mg. per dose, and again no change in body physiology was detected. This substantiated the views of others[17] who refer to its exceedingly low toxicity.

Sensitivity tests were conducted, using 0.002 mg. (0.2 c.c. of solution containing 10 μg per cubic centimeter) and the results can be noted in Table I.

TABLE I. HYALURONIDASE SENSITIVITY

	NO. TESTED	NO. POSITIVE	PER CENT
First product[10]	108	10	9.3
Second product	677	11	1.6
Later products	1,236	1	.08
Totals	2,021	22	1.08
Adults	205	2	1.95
Children	1,816	18	1

It can be noted that with the newer, more purified products, the allergic factor has been markedly reduced. As previously reported,[18] conjunctival tests were negative in all cases. This included one positive skin test, which led us to believe that, in this instance, skin tests were more reliable.

In order to determine the optimum amount of hyaluronidase to be used, the following experiment was carried out: Using an experimental preparation of the enzyme (second product, Table I) containing 125 viscosity units per cubic centimeter, a comparison was made between, on the one side, a dose of 25 viscosity units, and, on the opposite side, 50, 100, 125, 250 and 375 viscosity unit doses, respectively. Into each thigh 150 c.c. of 5 per cent glucose in saline were given and it was noted that the absorption capacity increased up to 100 viscosity units, at which point it took twenty-five to thirty minutes, while 125 to 375 viscosity units took about the same time. This was repeated on five other patients using a more concentrated solution of hyaluronidase (1,250 viscosity units per cubic centimeter) and again the best results ranged from 90 to 100 viscosity units per dose. Using the latter concentration, these tests were repeated using only 10 c.c.

of 5 per cent glucose in saline and 1 c.c. of 2 per cent procaine solution, respectively, and again 100 viscosity units appeared to be the most satisfactory. These results revealed that increasing the dose did not increase its effect in direct proportion, for beyond 100 viscosity units the increased spread of absorption was negligible.

These tests were repeated with the latest product.* The strengths tried, in viscosity units, were 125, 250, 375, 500, 625 and 750, respectively. It was noted that the best and most consistent results were obtained when utilizing 500 viscosity units. This is illustrated in Table II.

TABLE II. RELATION OF HYALURONIDASE DOSAGE TO ABSORPTION

AMOUNT USED (IN VISCOSITY UNITS)	ABSORPTION RATE (IN MINUTES)		
	1ST TEST	2ND TEST	3RD TEST
125	70		70
250	55	70	72
375	39	55	44
500	40	43	44
625	37		36
750	40	42	31

Thus there appears to be a discrepancy between the relationship of viscosity units to physiological activity when that activity of two types of hyaluronidase preparations[19] (small as opposed to large scale) was observed. Therefore, further laboratory and clinical studies should be undertaken to clarify the potency of the dosage.

Studies were done to determine the effect of hyaluronidase when added to adrenaline, procaine, penicillin, streptomycin, Parenamine and Benadryl. In every case absorption was facilitated. When using hypertonic solutions, the absorption was increased, but not as much as with isotonic solutions. This is shown in Table III.

TABLE III. RELATION OF HYALURONIDASE TO FLUID ABSORPTION

SOLUTION	NO HYALURONIDASE (AVERAGE TIME IN MINUTES)	HYALURONIDASE (AVERAGE TIME IN MINUTES)
Calcium gluconate 12 c.c. of 10 per cent sol.	80	30
Glucose 10 c.c. of 10 per cent sol.	60	27
Parenamine 5 c.c. (painful)		
15 per cent	23	13
7½ per cent	18	9
5 per cent	14	8
Benadryl .1 c.c. (painful and caused raised erythema)	28	13.5
Adrenalin	52.5	12.5
Procaine		9
Penicillin		7.5
Streptomycin	60	7
Saline		7

*Marketed as Alidase by G. D. Searle Co., Chicago, Ill.

The effect of hyaluronidase was also studied in patients with elevated temperatures, allergies, and rheumatic fever, and it was noted that absorption was hastened in all cases whether they were ill or not. The difference was insignificant, whereas in the "McClure-Aldrich Saline Test" absorption was more rapid in infectious cases. This gives the impression that there may be an increase of hyaluronidase formation caused by bacteria during illness, or perhaps a decrease in hyaluronic acid formation in the tissues, which increases the absorption of saline.

We used clysis with hyaluronidase in seventy cases, each one receiving 50 to 400 viscosity units of the experimental preparation (250-2,000 viscosity units of the commercial product), depending on the duration and severity of the case. The same area could be used for about five days if necessary, but usually was used only up to the third day, as its effect diminished thereafter. It was better to inject it through the rubber tubing just after the start of the hypodermoclysis. The best results were obtained during the first clysis, with gradually diminishing effect as others followed. In the average case utilizing hyaluronidase, 250 to 300 c.c. of electrolyte solution could be given rapidly within 80 minutes and other clysis could be given in fairly rapid succession. Without the addition of hyaluronidase, a similar amount of fluid would take 150 to 180 minutes, and the area could not be used for at least 8 hours afterward. This was substantiated by a recent report[15] where, in a comparison of absorption of similar amounts of fluid, it was found that the control solution had to be stopped on an average of four times because of swelling, induration, or pain. This was unnecessary when hyaluronidase was used. Six viscosity units of commercial hyaluronidase could take care of 10 to 50 c.c. of solution. The same area was used for as long as eight days in one case, but it was usually unnecessary to continue that long. The needles were kept in one position from one to five days. However, the tissues became inflamed about the point of insertion of the needle after the second day in most instances, so it was considered best to change the needle site every third day.

In addition, hyaluronidase facilitated absorption of plasma given subcutaneously in seven cases. This was even more effective when the plasma was diluted with saline in a ratio of 1:1. The length of time and quality of induration and pain were much less when hyaluronidase was used.

Subcutaneous blood was also given to six patients, both with saline and undiluted. The hemoglobin was raised slightly in four of the six cases. It was more effective when undiluted, for when diluted it probably also increased the volume and dilution of the circulating blood. It did not appear to be successful in cases where the bone marrow had been suppressed for any length of time. From the present observations, it could not be considered a feasible method for securing marked or rapid blood value elevations. Therefore, at this time, it cannot be recommended as a routine procedure, but should be used only when the giving of intramuscular blood is indicated.

Hyaluronidase was successful in all but two cases. In two infants with severe diarrhea the administered fluid (5 per cent glucose in saline in one and plasma in the other) formed a local pocket of boggy edematous tissue, and ab-

sorption ceased. Examination revealed a total protein of 3.8 per cent in one and 4.7 per cent in the other. In the first case, whole blood was given intravenously, raising the total protein to 5.5 per cent, and absorption was quickly resumed. In the other, as soon as plasma was given intravenously, the fluid was absorbed and no further trouble was encountered. These cases suggest that marked alteration in intracellular structures plus intercellular changes may hinder absorption with hyaluronidase and that the total proteins should be at least 5.5 per cent.

In an earlier report,[18] the effect of hyaluronidase was also studied in two cases of hydrocephalus. The material was given intraventricularly and although the skull circumference did not increase during this period, no definite conclusion could be reached.

The effect of hyaluronidase has been determined in two cases of the nephrotic phase of nephritis. It took 8 minutes for 0.1 c.c. of saline to be absorbed, while in the normal child it took 3 minutes. In reviewing the figures on cholesterol and proteins, it was noted that after administering hyaluronidase, the total proteins and free cholesterol fraction were slightly lowered, while in the normal children receiving the same dose, the total proteins, especially the albumin fraction and the free cholesterol, were raised. The significance of this result cannot be ascertained without further studies.

Hyaluronidase has also been found of value in local anesthesia in general surgery[20] by increasing the skin area anesthetized by 40 per cent. In addition, the same authors found it of value in infiltrative anesthesia in ankle sprains, subdeltoid bursitis, and myositis. They also noted that in sixty-five dental cases the anesthesia was more complete and more widespread than by standard methods.

In view of this and because some[21] advocate the use of combined penicillin and procaine to eliminate pain and secure the effectiveness of local penicillin therapy, it was deemed advisable to try this combination for local anesthesia with and without hyaluronidase. In three children 1 c.c. of 2 per cent procaine and 1 c.c. of saline containing 10,000 units of penicillin were given subcutaneously into each thigh. On one side, it was preceded by 0.08 mg. of hyaluronidase, and on the other side without any other substance. In both cases, the area of injection became red and inflamed and the diameter ranged from 1½ to 2 inches with the hyaluronidase against 1½ inches without it. On the side hyaluronidase was used, the absorption time was 6.5 minutes and the anesthesia was gone in 18 minutes, while on the other side absorption time was 17 minutes and anesthesia lasted 20 minutes. From these few observations, it was deduced that with the use of hyaluronidase the area of anesthesia was increased by 33.3 per cent, but the length of anesthesia was decreased by 16 per cent.

Hyaluronidase has been used[15] in the intramuscular method of pyelography and the results have been favorable in a small number of cases.

Recently it was also shown[21] that by adding hyaluronidase to penicillin before instilling it into the paranasal sinus, there was an increased penetration of the penicillin into the mucous membrane. However, an attempt[22] to use hyaluronidase to dissolve urinary calculi failed. Hyaluronidase was also instilled into one or two ears containing cerumen, with the other side acting as a control with

normal saline instillation. The ears were filled with the respective fluids and covered with cotton to prevent their easy escape. The procedure was repeated three times daily. It was tried in five cases with actual dissolution of from one-half to all of the wax. In view of the small number of trials, this phase is being further investigated before any specific recommendations can be made.

In an attempt to dissolve nasal mucus secretion with hyaluronidase, two children with marked viscid nasal discharge were given hyaluronidase solution intranasally three times daily. However, there was no evident success with this treatment.

It has also been shown that there are inhibitors[7, 24, 25] of hyaluronidase in the normal human plasma. Furthermore, other substances such as heparin,[7] chondroitin sulphate,[7] borate,[7] and salicylates[28] promote the action of serum on hyaluronidase. Meyers[7] states that all inhibitors are, or contain, acid polysaccharide.

In an attempt to check on the belief that salicylates act in rheumatic fever by controlling hyaluronidase, three patients were given various forms of salicylates on six different occasions, and the salicylate levels were taken at frequent intervals. The rate of absorption of hyaluronidase in saline was determined prior to taking each blood sample. These results are listed in Table IV.

From Table IV, it can be noted that in the majority of the tests, as the salicylate levels rose, the hyaluronidase absorption time also increased. This

TABLE IV. COMPARISON OF SALICYLATE LEVELS AND HYALURONIDASE ABSORPTION TIME

	SALICYLATE LEVELS (MG. PER 100 C.C.)						HYALURONIDASE ABSORPTION TIME (EXPRESSED IN MINUTES AND SECONDS)					
NO. OF TRIALS	1	2	3	4	5	6	1	2	3	4	5	6
Patient I												
Fasting	0	0	0	0	0	0	3:40	3:50	3:10	4:45		
½ hour	3.3	4.9	7.8	1.6	3.1	7.5	3:45	5:20		4:20	2:0	3:0
1 hour	4.9	8.5	8.7	2.8	4.9	11.1	6:0	5:45	4:50	4:00	3:0	4:0
2 hours	8.0	10.3	9.9	3.8	7.8	11.1	7:0	5:40	5:20	8:00	4:0	5:30
3 hours	13.6	14.3	11.5	4.2	8.2	10.4	8:0	5:30	4:10	6:00	5:0	5:30
4 hours	16.9	16.0	11.0	4.9	7.8	9.9	8:40	7:0	6:00	5:30	5:30	5:40
5 hours	17.9	15.0		5.2	7.5	9.6	7:20	5:55		6:10	6:0	6:0
6 hours	16.9	15.0		4.9	7.1	9.4	9:20	4:30		6:10		6:0
Patient II												
Fasting	0	0	0	0	0	0	3:50	4:00	3:20	5:0		3:0
½ hour	7.3	.71	.94	.94	1.2	1.6	3:50	4:28		4:40	2:0	4:0
1 hour	10.8	2.3	7.8	1.6	3.1	4.9	5:10	6:45	5:30	4:05	2:30	4:30
2 hours	12.7	6.6	11.5	3.5	5.6	10.1	6:20	6:40	5:30	6:00	3:30	6:00
3 hours	10.3	8.7	12.2	4.9	6.8	9.2	7:00	4:30	4:20	4:50	4:30	6:00
4 hour	11.5	11.0	11.7	5.2	5.6	11.1	7:20	7:00	10:00	5:00	5:00	6:30
5 hours	12.5	10.8		5.9	8.0	10.6	6:20	5:40		6:10	6:00	4:00
6 hours	10.3	10.3		6.6	8.5	12.0	6:50	5:40		6:00		
Patient III												
Fasting	0	0	0	0	0	0	3:40	3:50	3:10	4:45		2:30
½ hour	5.4	.47	.94	.71	0	0	4:00	4:10		4:25	3:00	3:00
1 hour	5.9	2.1	3.8	3.3	1.6	0	4:20	4:28	5:00	5:50	4:00	3:00
2 hours	7.5	4.2	6.8	6.6	5.4	0	6:20	6:00	5:20	4:50	4:30	4:30
3 hours	16.5	4.7	7.8	8.0	5.2	0	7:25	5:40	4:10	5:00	6:00	4:00
4 hours	15.7	5.9	10.2	6.8	5.7	0	7:40	6:30	6:00	4:45	6:00	3:00
5 hours	14.6	6.6		5.2	5.9	0	11:00	6:10		5:20	7:00	3:30
6 hours	14.6	5.9		5.4	6.3	0	10:00	5:00		5:00		

was not consistent, however, since with some high salicylate levels the increase was less than with some lower salicylate levels. There is a possibility that other physiological factors may have played a part. However, when a zero salicylate level persisted (as in test 6 of Case 3) the absorption time never exceeded 4½ minutes. On the other hand, with a salicylate level, the absorption time exceeded 5 minutes on one or more occasions during each test. From these observations it would appear as though salicylates have some antihyaluronidase activity, and this should be considered in conditions where such an effect is desirable.

SUMMARY AND CONCLUSIONS

1. Hyaluronidase facilitates absorption of fluids when used in a dosage of 500 viscosity units.

2. Its trial in eighty-three cases verified its efficacy.

3. When hyaluronidase was used with isotonic solutions, absorption was faster than with hypertonic solutions.

4. It hastens absorption of intramuscular blood but it does not result in sufficient and consistent hemoglobin increases to warrant its being recommended as the treatment in anemias at present.

5. Hyaluronidase was successful in all illnesses except when the total proteins were below 5.5 per cent.

6. No evidence of pathologic or physiologic changes could be attributed to its use.

7. Over-all sensitivity to the product has been 1.08 per cent, but with the latest product only 0.08 per cent have been allergic.

8. Its status in nephrotics and hydrocephalics is still uncertain.

9. Its use against nasal discharges was not encouraging, but it appeared to have a beneficial effect on aural cerumen.

10. It has been found of value for local anesthesia in surgery and dental work, and also for use in the intramuscular method of pyelography.

11. Hyaluronidase may be counteracted by certain drugs such as salicylates and also by elements in the blood.

12. In conclusion, it may be stated that the field of usefulness of this drug is just beginning, and it promises to become one of our more useful medicaments.

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METHYL TESTOSTERONE AND PLASMA FOR PREMATURE INFANTS

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THE use of methyl testosterone in premature infants has met with varying results. Shelton and Varden[1] administered it to a small group of premature infants and found it of value in decreasing the expected mortality rate and in shortening of the period of hospitalization. A later report[2] on a larger group of premature infants confirmed their first impressions, and in neither series were any untoward effects of the testosterone noted. Wilkins and Hardy,[3] using methyl testosterone, found no significant difference in weight gain between the premature infants and the controls. No untoward effects were noted in their series.

Laeble,[4] in using oral plasma as a supplemental feeding for premature infants, found that infants did better, there was less weight loss, less vomiting, and less gastric irritation. Quoting from White and Weinstein,[5] "Plasma aids the newborn premature to maintain weight, nutrition, fluid balance and prevent intercurrent infections and diarrhea." It was used subcutaneously and not orally in doses of 10 c.c. per pound of body weight daily for eight days.

In an effort to determine if a combination of methyl testosterone and plasma would be of benefit in the treatment of premature infants, a study was made of thirty-six premature Negro infants born in the Virgin Islands between June 1, 1948, and June 1, 1949. Two groups were studied with twenty-three in the first group and eleven in the second group. Two others fell into both groups and were not included in either group. In the first group, the diagnosis of prematurity was made on a weight of 2,500 Gm. or less alone, as no measurements were available; in the second group, the diagnosis of prematurity was made on a weight of 2,500 Gm. or less, a crown-heel length of 47 cm. or less, and a head circumference of 33 cm. or less.

All infants of both groups whose weight was 2,268 Gm. or less were put in incubators and remained until they attained this weight. All were given one cubic centimeter of vitamin K (2.4 mg. Hykinone) daily for three days and a hypodermoclysis of 50 to 100 c.c. of 2½ per cent glucose once or twice daily for one week, depending on skin turgor and weight. After the first week vitamins C and D were added to the formula and ferrous sulfate was added during the third week. The premature infants were started on one to 2 oz. of a stock formula (evaporated milk 7 oz., water 17 oz., Karo 1½ oz.) every three hours, depending on weight after the first forty-eight hours.

Group I was given 0.5 c.c. of crude liver extract intramuscularly every other day. Group II was given methyl testosterone 5 mg. in 10 A.M. feeding daily.

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In addition, the premature infants in Group II received 100 to 150 c.c. of plasma orally daily in divided amounts until they attained a weight of 2,722 Gm. The plasma was given by bottle or gavage, as was the formula.

TABLE I

GROUP I

NO.	SEX	BIRTH WEIGHT (GM.)	6 LB. (2,722 GM.)	GAIN (GM.)	NO. DAYS IN HOSPITAL	AVERAGE GAIN (GM.)	REMARKS
1	M	1,814	2,722	908	99	9	
2	M	1,701	2,722	1,021	90	11	
3	F	1,871	2,722	851	72	12	Abscess of scapula region
4	M	2,268	2,722	454	34	13	
5	F	2,295	2,722	427	35	12	
6	F	2,268	2,722	454	50	9	
7	M	2,327	2,722	395	38	10	Abscess of scapula region
8	F	2,268	2,722	454	47	10	
9	F	2,268	2,722	454	65	7	
10	M	2,438	2,722	284	26	11	
11	F	1,929	2,722	793	66	12	
12	M	1,929	2,722	793	120	7	
13	M	2,041	2,722	681	50	14	
14	F	2,211	2,722	511	101	5	
15	F	2,268	2,722	454	44	10	Transfusion
16	M	2,268	2,722	454	64	7	
17	M	2,296	2,722	426	44	10	
18	M	2,353	2,722	369	29	13	
19	F	2,381	2,722	341	36	9	
20	F	2,325	2,722	397	60	7	Transfusion
21	F	2,410	2,722	312	68	5	
22	M	2,438	2,722	284	52	5	
23	F	2,495	2,722	227	29	8	
Average		2,211			58	9	
24	M	2,155	2,722	567			
25	F	2,098	2,722	624	25	25	

GROUP II

NO.	SEX	BIRTH WEIGHT (GM.)	6 LB. (2,722 GM.)	GAIN (GM.)	NO. DAYS IN HOSPITAL	AVERAGE GAIN (GM.)	NO. DAYS RECEIVING TESTOSTERONE AND PLASMA
26	M	2,041	2,722	681	27	25	25
27	M	2,098	2,722	624	22	28	21
28	F	2,268	2,722	454	37	12	24
29	F	2,353	2,722	369	20	18	18
30	F	2,381	2,722	341	7	49	9
31	M	2,466	2,722	256	14	18	17
32	M	2,495	2,722	227	19	12	16
33	M	2,338	2,722	384	21	18	14
34	F	2,244	Died seventh hospital day				
35	M	2,099	2,722	623	31	20	29
36	F	1,418	2,722	1,304	54	24	50
Average		2,200			25	12.5	

DISCUSSION

In Group I, the average daily weight gain was 9 Gm. and the average hospital stay was fifty-eight days. (If the eleven best cases were selected as controls, the average daily weight gain would be 11 Gm. and the average hospital stay forty-eight days). The number of days necessary to regain birth weight

varied from five to fifty-four days, averaging fourteen days. The ultimate mortality rate was not known, as records were not available. Two of the Group I premature infants developed abscesses of the scapula region following subcutaneous fluid therapy. Two received one transfusion each of 20 c.c. of whole blood (No. 15 and No. 20).

In Group II, of twelve cases, one premature (No. 34) died on the seventh hospital day of aspiration pneumonia following gavage feeding. The average daily weight gain of the remaining eleven was 22.5 Gm. and the average hospital stay was twenty-five days. The number of days to regain birth weight varied from zero to five days, averaging two days.

No. 24, not included in either group, weighed 2,155 Gm. at birth, and on the fifty-second hospital day weighed 2,061 Gm. At this time he was started on methyl testosterone 5 mg. daily and 150 c.c. of plasma. On the seventy-seventh hospital day, his weight was 2,122 Gm., for an average gain of 26 Gm. a day after starting plasma and testosterone. No. 25, also not included, weighed 2,098 Gm. at birth, and on the tenth hospital day weighed 2,070 Gm. He was then started on testosterone and plasma. On the twenty-fifth hospital day he weighed 2,722 Gm.

No. 28, in Group II, developed a diarrhea on the sixth hospital day which lasted for twelve days. Testosterone and plasma were stopped and started again on the nineteenth hospital day, at which time the weight was 1,928 Gm. No. 33 developed a diarrhea which lasted five days but plasma and testosterone were continued. Causes of both diarrheas were not determined. Cultures were negative. No. 35 developed a gonorrheal infection of the right eye.

All premature infants were continued on testosterone and plasma until they reached 2,722 Gm., at which time these were stopped and the patients discharged. All of Group II were followed weekly in the Well Baby Clinic. There was no weight loss on first return visit to clinic. None of these showed any apparent enlargement of genitalia or breasts, and no hoarseness or abnormal hair growth. All were gaining weight normally after 150 to 180 days, and none had developed any jaundice. Plasma was obtained from Red Cross stock left to the hospital by the army.

Although only thirteen cases received plasma and testosterone in all, an appreciable difference in weight gain and shorter hospital stay are noted. In a hospital well-equipped to take care of premature infants, this treatment probably is not warranted, but in small, poorly-equipped hospitals it may be of some value. In the Municipal Hospital of St. Thomas where this work was done, there was but one graduate nurse on eight hours a day for five days a week, and only two wards helpers to take care of both premature and newborn nurseries.

SUMMARY

1. Two groups of thirty-six premature infants were studied.

2. Group I, the premature infants treated with usual premature nursery procedures, gained an average of 9 Gm. daily, and remained in the hospital an average of fifty-eight days.

3. Group II, the premature infants treated with methyl testosterone and plasma added to formulas, gained an average of 22.4 Gm. and remained in the hospital for an average of twenty-five days.

Acknowledgment is made to Dr. John Moorhead, Commissioner of Health of the Virgin Islands, who made this study possible.

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Case Reports

ADRENAL CYSTS AND ADRENAL INSUFFICIENCY IN AN INFANT WITH FATAL TERMINATION

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ADRENAL insufficiency in children and infants is becoming a more widely recognized syndrome. Butler, Ross, and Talbot[2] described the symptom complex of macrogenitosomia with signs of adrenal failure, and other authors[4, 18] have reported similar cases. A temporary insufficiency has been postulated by Jaudon,[8] and several such cases have been reviewed.[9] Idiopathic degeneration of the adrenal glands has been observed and reported.[1]

This paper describes the case of an infant with signs of adrenal insufficiency in whom autopsy demonstrated adrenal cysts.

CASE REPORT

R. C. was born in another hospital on June 1, 1948, spontaneously at term, the second child of healthy white parents. Pregnancy and delivery from a vertex position were uncomplicated. Birth weight was 3,320 Gm. On the day of birth he was examined by one of us, who noted that the scrotum was darker than usual. While in the nursery he had loose stools on several occasions. He was discharged on the eighth day of life weighing 3,120 Gm. At home his stools were formed and hard.

The evening before admission his stools became watery and green and he vomited once. Diarrhea and lethargy increased and he was therefore admitted to the contagious disease ward of this hospital on June 18, 1948.

Physical examination at that time showed only marked lethargy and moderate dehydration. His weight was 2,730 Gm. His skin was dark, especially that of the scrotum. Complete blood count showed only hemoconcentration, and the carbon-dioxide combining power was 20 volumes per cent.

The infant was placed on a routine treatment for diarrhea consisting of starvation for twenty-four hours, and parenteral fluids, saline, glucose, and sodium lactate to correct acidosis and dehydration. His stools became normal, and oral feedings with water and calcium caseinate (Casec) were started on the second day. In the absence of vomiting and diarrhea, despite theoretically adequate fluids by mouth, he remained dehydrated. This discrepancy was the outstanding characteristic of his illness.

A week later the patient looked much worse. His color was gray and he was very lethargic. The carbon-dioxide combining power was 33 volumes per cent, the serum sodium was 132 meq. per liter, and the serum potassium was 6 meq. per liter. Because of the poor clinical appearance, and before these reports were obtained, he was started empirically on adrenal cortical extract (Eschatin, Parke Davis & Company), 0.5 c.c. every four hours. Oral feedings were discontinued and venesection was done. Intravenous therapy was con-

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tinued for several days. The adrenal extract was increased to 0.75 c.c. every four hours after three days. There was only slight improvement and oral feedings were reinstituted.

At the end of his third hospital week he began to vomit and pass loose stools and his condition became critical. Darrow's solution was given by mouth and parenteral fluids were administered intensively up to 750 c.c. per day. Intramuscular penicillin, 10,000 units every three hours given since admission, was continued. On his thirty-fifth day of life he weighed only 2,360 Gm.

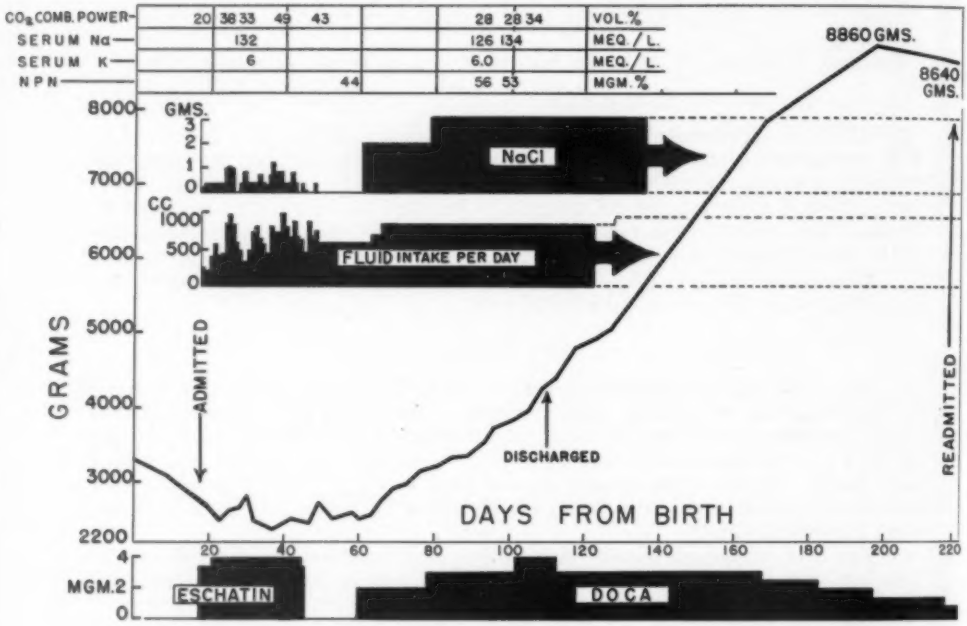

Fig. 1.—A graphic representation of the course of R. C. from birth to death, showing the relationship between the administration of desoxycorticosterone acetate and the weight gain.

In spite of his poor condition, further investigative procedures seemed imperative. Chest x-ray was normal. Bilateral subdural taps encountered no accumulation of fluid. Stools were examined for fat and starch with negative results. Duodenal drainage obtained secretions with normal trypsin activity. Urine was collected for twenty-four hours and amounted to 360 c.c. with a specific gravity of 1.003. Because of the possibility of intestinal allergy, a Nutramigen formula was started. The stools remained green, though formed. His formula was increased gradually in strength and amount, and by July 12 he was taking 380 calories (152 calories per kilogram). The adrenal extract was stopped on July 13. Skin turgor was poor even with 200 c.c. of fluid per kilogram daily. After six weeks of intensive treatment he weighed only 2,500 Gm.; he was a pitiful sight.

It was then that Jaudon's article[9] on adrenal insufficiency was published. We felt that this patient fitted into his group since he had never been hydrated, was grayish in color, had gastrointestinal symptoms, and seemed to be getting steadily worse. On July 30 he was started on 2.0 mg. desoxycorticosterone

acetate (DOCA) subcutaneously, and 2.0 Gm. of salt in his formula daily. The results were dramatic, as can be seen from the chart. Within three weeks he gained over 700 Gm. The same Nutramigen formula was continued, providing 668 calories per day. During the second week of DOCA therapy he seemed to improve more slowly, and the DOCA was increased to 3.0 mg., and the salt to 3.0 Gm. daily. He again improved, became active, smiled, and his cry became lusty. On Aug. 30, a blood count showed an eosinophilia (17 per cent of 11,900 white blood cells). His serum sodium was 126 meq. per liter and the serum potassium was 6.0 meq. per liter. The carbon-dioxide combining power was 28 volumes per cent. However, his clinical appearance belied these chemical findings. A week later the sodium was 134 and the eosinophilia had dropped to 8 per cent of 13,000 white blood cells. By the end of another week the differential count was normal. He developed catarrhal otitis media several times which responded to intramuscular penicillin. The DOCA was increased to 4.0 mg. on September 8 and reduced to 3.0 mg. on the twenty-third.

He was discharged on the one hundred and eighth hospital day, four months old, weighing 5,000 Gm. His mother was instructed in the administration of subcutaneous medication. She was to give 1.5 mg. of DOCA twice a day, and 3.0 Gm. of salt daily.

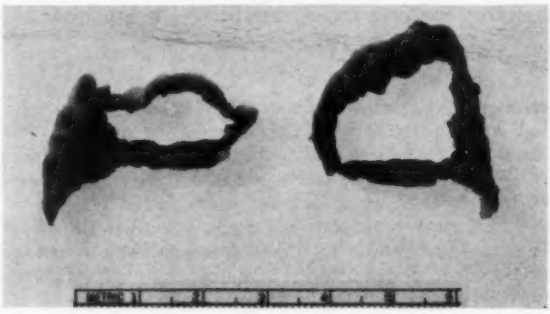

Fig. 2.—Sections of the adrenal glands of R. C.

At home he continued to develop normally. He weighed 7,870 Gm. at 5 months of age. The DOCA was reduced to 2.5 mg. daily, and two weeks later it was further reduced to 2.0 mg. The extra salt was continued, 3.0 Gm. daily. On December 15 he weighed 8,860 Gm., and the DOCA was lowered to 1.5 mg. per day. The final reduction to 1.0 mg. was made on Jan. 5, 1949. Throughout all this time he had been fine and was eating a general diet.

For lunch on January 7 he was given banana for the first time, and shortly thereafter he began to vomit. The vomiting continued throughout the afternoon, and he had two loose stools. He was readmitted to the hospital that evening at 7 P.M.

Physical examination showed a healthy, robust infant weighing 8,640 Gm. with a rectal temperature of 38.9° C. The tympanic membrane on the left was slightly injected. Skin turgor was good, and the genitalia appeared normal.

Intramuscular procaine penicillin was given for the ear infection. Four hours later he seemed lethargic and had two loose green stools. A hypodermoclysis of 100 c.c. normal saline was given. At 4 A.M. the next morning the temperature had risen to 41° C. and he was dehydrated and semicomatose. Another 100 c.c. clysis of normal saline was given. Before DOCA could be

given his heart rate rapidly increased, heart sounds became distant, shock deepened, and he died.

A complete post-mortem examination was performed five hours after death. The pertinent portion of the protocol was as follows:

"The left adrenal weighs approximately 10 Gm., and measures 4.5 × 2.5 × 1.5 cm. It is tan in color and its surface is finely lobular. The gland is moderately firm and on section there is a cyst occupying about three-fourths of the diameter of the gland and containing a small amount of brown fluid. The shell of the gland measures 0.4 cm. in thickness.

"The right adrenal weighs approximately 10 Gm., measures 4.5 × 3 × 1.5 cm., and is tan in color and similar to the left adrenal except that its center is composed of two cysts. [See Fig. 2.]

"*Microscopic Examination.*—The three layers of the cortex, i.e., zona glomerulosa, zona fasciculata, and zona reticularis, can be differentiated and do not appear remarkable. There is a cystic space in each adrenal gland lined by compressed cortical cells and a smooth, thin, fibrous membrane. Several other but smaller cysts are present within the cortical substance. They contain eosinophilic coagulated fluid. Histologically there is a sufficient amount of cortex present to maintain life.

"*Bacteriological Examination.*—Culture (from left middle ear) yields mixed flora including *Bacterium coli*, *Streptococcus viridans* and *Micrococcus tetragenus.*"

DISCUSSION

In this case adrenal insufficiency was not suspected early, although adrenal extract was tried empirically during the first month of life. The insufficiency was probably present from birth. The pigmentation of the scrotum and the tendency to gastrointestinal disturbances suggest this. The doses of adrenal extract given were too small to have had any therapeutic effect.

Certain other laboratory procedures would have been of great interest and importance in diagnosis, but for technical reasons they could not be done at the time. The two most desired were 17-ketosteroid excretion, and eosinophil counts as described by Thorn, Forsham, Prunty, and Hills.[16]

Cases of adrenal insufficiency with macrogenitosomia have been reported frequently. Butler, Ross, and Talbot[2] first described this syndrome in an infant with brownish pigmentation of the skin who went into collapse on fluid and salt restriction. Their patient had increased estrogen and androgen excretion. Wilkins, Fleischmann, and Howard,[18] Dijkhuizen and Behr,[5] Thelander and Cholffin,[15] Darrow,[4] and a report from New York Hospital-Cornell Medical Center[11] describe similar cases. Darrow pointed out that such androgenic hyperplasia may or may not be accompanied by adrenocortical insufficiency.

In 1946 Jaudon[7] postulated the existence in infants of a syndrome of temporary adrenal insufficiency such as is seen with other endocrine glands. This symptom complex was further evaluated in 1948[9] when he added five new cases. These patients presented signs of adrenal insufficiency and responded to treatment with DOCA. Ultimately the DOCA was withdrawn completely. This is the group to which it seemed the present case belonged.

Our case differed from those of Jaudon clinically in that DOCA therapy never completely corrected the lowered serum sodium level. The highest level determined was 134 meq. per liter and this was after a dramatic clinical response. This inability to correct the altered electrolytes may have presaged the ultimate fatal termination.

The true nature of the adrenal cysts is not known. It can be predicated that prenatally or during delivery there occurred a destructive lesion, all signs

of which were lost and its place indicated by a cyst. LeComte, as quoted by Pearse,[12] collected cases of adrenal hemorrhages in newborn infants, thirty-three bilaterally, eight on the right, and eleven on the left. He felt that if these were not absorbed and the infant survived, they became encapsulated as hematomata. One wonders whether our patient would have survived if replacement therapy had been continued without reduction of dosage, or if he had escaped intercurrent infection. The amount of cortical tissue remaining might have been ample for life, if fully functioning, but for the added stress of infection.

The occurrence of adrenal cysts in infants and children has infrequently been reported. Campbell[3] mentioned seven cases at Babies Hospital in children under 5 years of age. In none of these was there any evidence of endocrinopathy. Most adrenal cysts at any age seem to be incidental post-mortem findings[10, 13] Review of the literature discloses only one case in an infant similar to ours. In 1888 Tyson[17] quoted Belaieff as having a case of a male infant with grayish discoloration of the skin. In spite of good intake he became weaker and died at 2 months of age. Necropsy showed numerous cysts of both adrenal glands. Schmieden and Peiper[14] reported a 5½-month-old infant with a blood cyst in a malignant tumor. This patient had no endocrinopathy.

SUMMARY

A case of congenital adrenal insufficiency is reported. Replacement therapy with desoxycorticosterone acetate permitted survival for seven months. Sudden death followed a minor infection. Necropsy showed bilateral adrenal cysts surrounded by normal appearing cortical tissue.

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AN UNUSUAL CASE OF HEMORRHAGIC DISEASE IN AN INFANT

(Probably Atypical Hemophilia)

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THE trend of the hemorrhagic diatheses is usually reasonably classified under one of a triad of causes, viz.: (1) deficient coagulability; (2) thrombocytopenia; and (3) vascular dysfunction. Nevertheless, there are instances of excessive bleeding and purpura which, due to unusual manifestations, are difficult to classify clinically or pathologically. Such an instance was recently observed in the pediatric service of the Royal Victoria Hospital, one which has eluded diagnosis as a known clinical or pathologic entity. Because of several atypical manifestations exhibited in this instance of hemorrhagic disease, it is reported in detail:

G. B., a male infant 18 months of age, was admitted to the pediatric service of the Royal Victoria Hospital May 25, 1948, for investigation of bruising and bleeding. At 6 months of age his parents first noted that when he had been sucking his thumb this digit became swollen and blue. Thereafter frequent bruising was noted; numerous ecchymoses appearing over his forehead, trunk, arms, and legs. At 16 months of age his mouth was injured after a fall from his cradle with profuse bleeding from the site of injury of such severity that blood transfusions were given as a life-saving measure. There had been no injury or abnormal bleeding at birth. The patient had had none of the contagious diseases of childhood or immunizations against them. The diet had been adequate with supplement of vitamins C and D. The family history revealed that approximately ten days prior to the mother's menses firm blue areas appeared in the skin of her thighs and legs, these disappearing shortly after the onset of the menstrual flow. A paternal uncle had occasional nosebleeds. None of the patient's three sisters or brothers exhibits a purpuric tendency. Physical examination revealed a well-nourished and well-developed white male infant with ecchymoses of varying sizes in the skin over the trunk and extremities. The spleen was easily palpable 3 cm. below the left costal margin. A small umbilical hernia was present too.

Hemogram, May 25, revealed 4,530,000 red blood cells, 87 per cent hemoglobin, 14,400 white blood cells, 310,000 platelets, prothrombin time of 18 seconds (normal), Rumpel-Leede test negative, coagulation time, 6½ minutes (retraction present), and bleeding time, 1½ ? minutes.

On June 7, blood was withdrawn from the right cubital vein. Later, purpuric spots were noted, followed by hemorrhagic extravasation into the soft tissues of the right upper extremity. Within a period of forty-eight hours continued extravasation of blood had caused a massive hematoma from the wrist to the shoulder joint. The hemoglobin fell from 8.7 to 3.8 Gm. per cent in ninety-six hours. It was feared that the patient would lose his right arm, yet the radial pulse remained and during the following three weeks the extravasated blood was gradually resorbed and the extremity appeared normal. The patient's severe anemia was corrected by transfusions with whole blood. The exact nature of the patient's bleeding was not understood and rutin 20 mg. three times daily, snake venom ½ c.c. (1:3,000 sol.) and ascorbic acid 100 mg. were all given daily.

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The patient recovered from this alarming episode, nevertheless continuing, intermittently, to have groups of firm, nodular, apparently spontaneous hemorrhages deep in the skin, which later manifested themselves as ecchymoses. These disappeared within a period of ten to fourteen days. Later during hospitalization the patient had varicella, the onset of which was associated with several, generalized, clonic convulsive seizures, and pertussis, during which, for the first time, the patient had frequent bouts of epistaxis. These epistaxes have continued since recovery from pertussis.

After the patient had recovered from the large hemorrhage into the right upper extremity, hematological studies were resumed. Repeated estimations of the bleeding time revealed it to be greatly elevated, on occasions the blood continuing to ooze from the site of puncture up to forty-eight hours or until controlled by an adrenalin (1:1,000) swab followed by a smear of Collodion and a gauze pressure-dressing. On one occasion considerable bleeding occurred into the soft tissues of the left forearm after a small stab wound (Fig. 1).

Fig. 1.

Because of the prolonged bleeding time in the presence of abundant platelets and an apparently normal clotting time, the disease was considered to be one like the disorder classified by Dameshek and associates[2] as "pseudohemophilia," in which the only abnormal finding is a persistently prolonged bleeding time. Nevertheless, repeated estimations of the coagulation time revealed it to be elevated, as well as the bleeding time.

Hence, there are two abnormal findings to be explained, viz.: the prolonged bleeding time and the prolonged coagulation time. There has never been a thrombocytopenia; the blood Wassermann reaction is negative; scurvy has been eliminated. The patient has received intensive study to eliminate the excessive bleeding as an allergic manifestation. The only plausible explanation for the prolonged bleeding time appears to be that of MacFarlane[1] and of Perkins[3] who, in athrombocytopenic purpura, or pseudohemophilia, demonstrated that an altered reaction of the capillaries to injury allowed the capillaries to dilate with extravasation of blood instead of effecting hemostasis by immediate constriction.

Deficiency in the blood of prothrombin, fibrinogen, platelets, and calcium have all been eliminated as causes of the prolonged clotting time. The blood

TABLE I

DATE	BLEEDING TIME	CLOTTING TIME (LEE-WHITE)	PRO-THROM-BIN TIME	FIBRIN TIME	RUMPEL-LEEDE TEST	PLATELETS
May/48*	1½ min.†	6½ min.	normal	normal	negative	310,000/cu.mm.
June & July/48	Patient ill with massive hemorrhage into soft tissues of right arm					
August/48	35 min.+	–	–	–	negative	–
Sept./48	11-13 min.	12 min.	–	–	negative	230,000/cu.mm.
Oct./48†	8½ min.	28 min.	normal	normal	negative	210,000/cu.mm.
Nov./48	30 min.+	24 min.	normal	normal	negative	–
Dec./48	–	19½ min.	–	–	–	–
Jan.-Feb. 14 1949	Patient ill with varicella and pertussis					
Feb./49	–	18 min.	–	–	–	–
Mar./49	–	32 min.	–	–	–	–

*Serum fibrinogen 0.336 Gm. per cent.
†Serum fibrinogen 0.280 Gm. per cent.
Serum Vitamin C 0.70 mg. per cent.
Serum Calcium 11.75 mg. per cent.

has been tested for excessive heparin and other anticoagulants, but none has been demonstrated. Rather, there appears to be a deficiency in the blood of a substance essential for normal coagulation, as a direct transfusion of small quantities of compatible whole blood (20 c.c.) to the patient reduced the clotting time to normal within one and one-half minutes. Citrated blood also exhibited the property of temporarily reducing the clotting time, yet this effect was appreciably less and of shorter duration than with fresh uncitrated blood. Taylor[4] has pointed out that the antihemophilic activity of both blood and plasma gradually disappears when preserved even at refrigerated temperatures. A direct transfusion of compatible hemophilic blood (clotting time 180 minutes) did not appreciably alter the clotting time of the patient's blood. The addition of thromboplastic substance to the patient's blood (in vitro) effected prompt coagulation. The intravenous injection of antihemophilic globulin (Fraction I of Cohn) did not alter the coagulation time, although the age of this particular substance probably reduced its efficaciousness.

TABLE II. SHOWING EFFECT OF BLOODS ON PATIENT'S CLOTTING TIME

A. 20 c.c. of uncitrated blood (intravenously) reduced clotting time from 19½ to 3½-7½ minutes.
B. 18 c.c. of citrated blood (more than twenty-four hours old) reduced clotting time from 18 to 9-18½ minutes.
C. 40 c.c. of hemophilic blood (uncitrated, clotting time 180 min.) reduced clotting time from 26-32 to 16-21 minutes.

With the above evidence it would not appear entirely unreasonable to assume that this is a case of hemophilia, though atypical and unusual in several features, viz.: (1) associated with a prolonged bleeding time; (2) the absence of a family history of hemophilia; (3) the observation that on several occasions the coagulation time was within normal limits or only slightly elevated. Birch[5] has reported that patients with hemophilia will occasionally exhibit a normal coagulation time; however, Davidson and associates,[6] reporting on a series of forty patients, failed to observe any who had exhibited a normal clotting time. A similar case with a prolonged clotting time associated with a prolonged bleeding time has been noted by Dameshek and associates.[2]

This case is interesting not only because of the unusual features and difficulty in diagnosis and classification, but also because of the questions that arise. Are all cases of hemophilia "hereditary" in that they have a definite genetic

background, or are there instances of hemophilia in which heredity plays no part? Certainly opinion in regard to hemophilia and to the role of platelets in that disease in particular has been modified in the light of recent findings. Evidence now favors a deficiency of the plasma globulin.[7] Quick[8] presents evidence to show that the hemostatic dysfunction in hemophilia is due to a lack of inactive "thromboplastinogen," a precursor to active thromboplastin. The platelets, functionally normal in hemophilia, are the activator of the inactive "thromboplastinogen." Other reports favor the presence of an antithrombin[9] or an antithromboplastin[10] as the fundamental abnormality in hemophilia. Possibly they are all responsible in certain instances.

The abnormal features in this case have been consistently observed over a period of months, and it is felt that, by definition, it cannot be a case of hemophilia or pseudohemophilia, though it has features of both. Nevertheless, it seems to be closely related to hemophilia, and if not an instance of that disease, what is it?

SUMMARY

1. An unusual case of hemorrhagic disease in an infant is presented.

2. The findings are not completely characteristic of either hemophilia or pseudohemophilia, although the case exhibits certain of the features common to both.

3. It is proposed that this disease is actually one of atypical hemophilia and its etiology is briefly discussed.

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DIAPHRAGMATIC HERNIA THROUGH THE FORAMEN OF MORGAGNI

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CONGENITAL hernia may occur in one of three parts of the diaphragm: (1) in either posterolateral portion, along the old pleuroperitoneal canal (the foramen of Bochdalek), (2) at the esophageal hiatus, or (3) in the retrosternal area (the foramen of Morgagni).

Hernias at the foramen of Bochdalek are by far the most common, more frequently on the left side, and, in 90 per cent of cases, do not possess a sac. The esophageal hiatus hernias always have a sac and are the next most common, while hernias at the foramen of Morgagni may or may not possess a sac and are extremely uncommon.[1] The infrequency of the subcostosternal (Morgagni) type is indicated by a recent report by Harrington[2] of 404 proved diaphragmatic hernias. Of this series, only eight came through the foramen of Morgagni. Previous to Harrington's report, eighty (not all proved) cases had been collected from the literature up to 1941.[3, 4]

The report of the case below is stimulated by several interesting facts: (1) a prolonged history of frequent alarming attacks in a child, which provoked the diagnosis (e.g., aspiration of foreign body) far afield from the true condition; (2) the worrisome statement of Johnson in a recent report[5] that the meager literature on this subject contains far too many diagnoses "proved by necropsy"; (3) the fact that, if alerted to the possibility, the physician can easily prove the diagnosis and apply a simple and curative procedure; and (4) the fortunate collection in this case of accurate roentgenological evidence which is believed to be of instructive value when chronologically illustrated.

CASE REPORT

J. B., a 2-year-old white boy, was brought to the North Richland Pediatric Clinic in mid-August, 1948, with the presenting complaint of alarming paroxysmal cough lasting five to ten minutes and accompanied by cyanosis and "choking."

The past history revealed an entirely normal birth, development, and weight gain despite a "digestive disturbance" since birth. During the child's first year he had had frequent attacks of "cramping" accompanied by mild to moderate coughing. Frequently his mother heard and felt gurgling sensations in the right chest. Part of nearly every feeding during this first year was vomited. There was extreme restlessness and fussiness and usually increasing restlessness preceded a vomiting spell which apparently allowed easier breathing and permitted sleep. There was no hematemesis and the bowel motions were normal.

During the week preceding admission to the hospital, three severe coughing-vomiting attacks had occurred, lasting from five to ten minutes. The child became blue and fought for breath. On each occasion he was held over his mother's shoulder and his back slapped with eventual relief. Although the child had been brought to physicians many times because of his "cough," the alarming progression of symptoms stimulated the parents to seek exhaustive study for diagnosis and definitive treatment. It was their fearful opinion that he might suffocate in his next attack.

From the Departments of Surgery and Pediatrics, Kadlec Hospital, Richland.

Fig. 1.

Fig. 2.

Fig. 1.—Routine chest plate showing lesion in right lower chest first thought to be caused by aspiration of foreign body causing partial atelectasis and pneumonia of the right lower lobe.

Fig. 2.—Lipiodol instillation film. No bronchial obstruction seen.

Fig. 3.

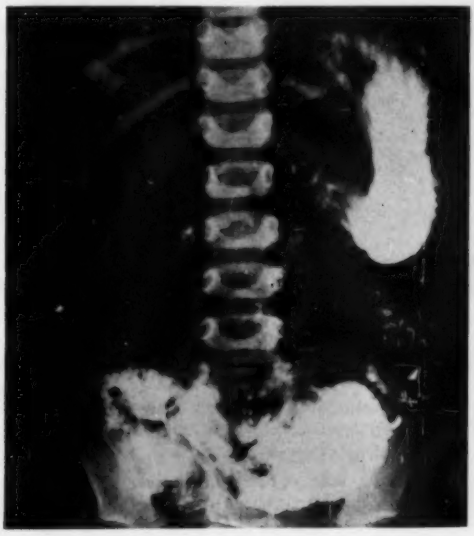

Fig. 4.

Fig. 3.—Lateral view, Lipiodol instillation film. Here the first clue of gas-filled loops in the chest (arrows) is seen. Some Lipiodol passed through the esophagus and is seen puddled in the stomach.

Fig. 4.—View taken soon after ingestion of barium showing normal stomach. (Barium is seen in colon as the gastrointestinal series was done following disclosure of normal colon by barium enema.)

The child was admitted to the Kadlec Hospital on Aug. 28, 1948. Physical examination, including the chest, revealed no significant abnormalities. Urine analysis, complete blood count, differential count, and hemoglobin were likewise normal. Tuberculin patch test was negative. An x-ray of the chest taken before admission was read as "Pneumonia, right lower lobe with possible partial atelectasis. Unable to exclude a foreign body obstruction" (Fig. 1). Fluoroscopy added no new facts. On Aug. 31, 1948, bronchoscopic examination was done. No foreign body or other abnormality of the bronchi was seen. Lipiodol studies (Fig. 2) were done and no obstruction was encountered. A lateral x-ray at this time aroused suspicion that there might be gas-filled loops in the chest, reaching this area through a retrosternal gap (Fig. 3). On Sept. 1, 1948, a barium enema was done revealing no abnormality. On the same day a gastrointestinal series was performed and the esophagus and stomach appeared normal (Fig. 4). The barium was then followed through the intestinal tract and at the end of three hours some barium appeared above the right diaphragm in the

Fig. 5.

Fig. 6.

Fig. 5.—Four hours after ingestion of barium. It is now evident that there is small intestine above the diaphragm.

Fig. 6.—The portal of entry to the chest (foramen of Morgagni) is easily seen in this lateral view four hours after barium ingestion.

region of the mass first noted in the right lower chest. At the end of four hours there was considerable barium in this region, outlining several loops of small bowel above the diaphragm anteriorly, principally on the right (Fig. 5). A lateral view at this time showed that the bowel could be traced through an opening anteriorly between the extreme anterior part of the diaphragm and the anterior abdominal wall (Fig. 6). Thus, the diagnosis of diaphragmatic hernia, most likely through the foramen of Morgagni, was established.

Preparation for operation consisted of prophylactic chemotherapy (penicillin), cleansing, and deflating measures of the gastrointestinal tract, routine skin preparation, sedation, and the insertion of a small Levine tube in the

stomach on the morning of operation. A high right rectus incision was made and the rectus muscle was displaced laterally. Exploration revealed: (1) a diaphragmatic hernial sac just under and to the right of the sternum, about 10 cm. in diameter with an opening ring 3.5 cm. in diameter, (2) the sac wall was definite, (3) the sac was empty at the time of operation except for a "pinched" 5 cm. portion of the anterior part of the left lobe of the liver, (4) all the intestines were in the abdomen, and (5) the abdominal cavity was "roomy." The liver was reduced into the abdomen without difficulty and the sac was then everted into the abdomen and its neck closed with a suture ligature of medium silk and the redundant portion excised. The edges of the hernial ring were then denuded and the diaphragmatic muscle edges were approximated with mattress sutures of medium silk. The abdomen was then closed in layers.

The postoperative course was smooth; the Wangensteen suction and oxygen tent previously ordered were discontinued after twelve hours. A fluid diet was thereafter easily tolerated and ambulation started on the third postoperative day. After removal of the skin sutures on the seventh postoperative day, the patient was discharged.

An x-ray taken on the afternoon of the operative day revealed an absence of the previous right chest abnormality; the diaphragm margins were normal. There have been no recurrences of symptoms.

COMMENT

Like any other unusual disease, the most proper prerequisite for the diagnosis of congenital diaphragmatic hernia is suspicion. Even so, as illustrated in the case reported, extensive study is often necessary. Bronchoscopy, bronchography, barium enema, and even gastrointestinal series were of little help until a four-hour plate was taken which showed small intestinal loops filled with barium above the diaphragm. The lateral view indicated that the less common foramen of Morgagni admitted the intestine, rather than the foramen of Bochdalek. The diagnosis of all diaphragmatic hernia rests essentially on an exhaustive work-up in patients having peculiar respiratointestinal symptoms.

As regards treatment of congenital diaphragmatic hernia, there are three factors worthy of note: (1) The thoracic approach is far less satisfactory (in infants and children) than the abdominal approach. Through the latter, reduction is easier and a two-stage closure, if necessary (in case of "shrunken" abdominal cavity), is possible. (2) When the hernia is thought to be extensive, the phrenic nerve should be crushed so that: (a) more room will result in the abdomen as the diaphragm rises, (b) it will be easier to work on a resting diaphragm, (c) the diaphragm will not tend by its motions to pull away from its suture line. (3) Positive-pressure anesthesia must always be provided for as occasionally, as Ochsner[6] has shown, a communication exists in the anterior mediastinum and exposure of one pleural cavity to atmospheric pressure may result in bilateral pulmonary collapse unless positive pressure from above is present.

SUMMARY

1. The types of congenital diaphragmatic hernia are listed and the relative frequency of each is mentioned.

2. A case of diaphragmatic hernia is reported and x-rays reproduced in chronological sequence.

3. Comment is made on the difficulties in the diagnosis of congenital diaphragmatic hernia and precautions to be taken as regards treatment.

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EPIPHYSEAL DESTRUCTION BY FROSTBITE

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IN July, 1949, a boy of 9 years appeared for examination because of pain and swelling of the digital joints of the right hand. Approximately two and one-half years previously, when in an automobile accident in North Dakota, the boy had sustained a severe enough frostbite of the right hand to make amputation a suggested possibility. On examination now, the fingers of the right hand are shorter than those of the left, and the distal and middle joints are flattened and thickened. The fingernails are normal; motion is present and not painful except on rather vigorous manipulation. At room temperature the skin color remains normal and circulation apparently adequate. On chilling the hand becomes blue and the boy says it aches. The lad presents no other abnormalities. The x-ray picture of both hands is shown in the accompanying figure. It will be noted that the epiphyses of the distal and middle articulations of the second to fifth digits are missing and the diaphyses are roughened with thinning of the

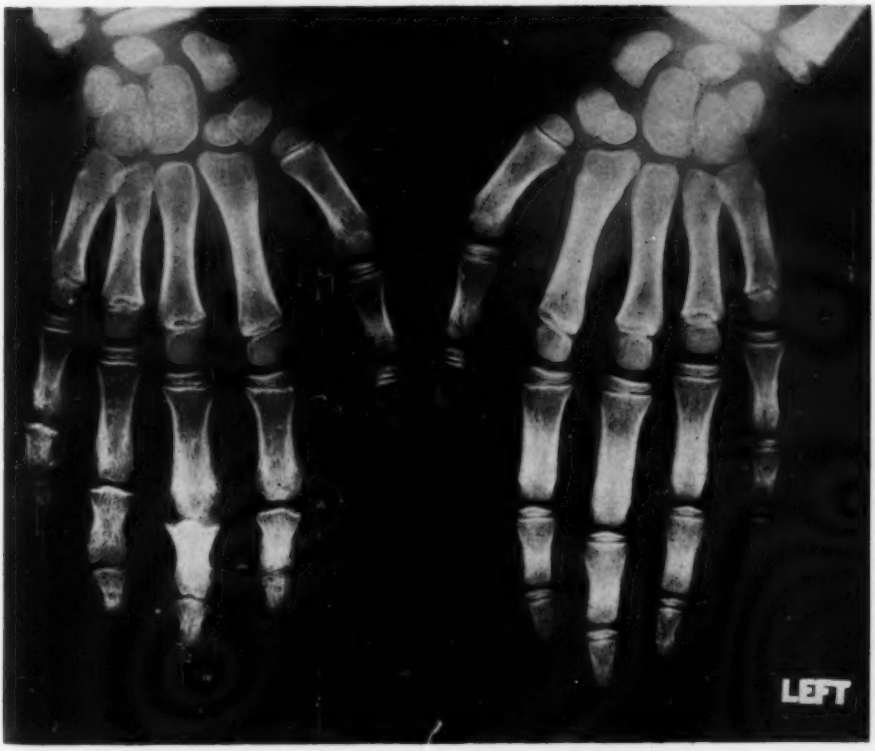

Fig. 1.—X-ray of 9-year-old boy's hands, showing missing epiphyses and roughened diaphyses with thinning of the cartilages. Note right hand is smaller than left.

From Children's Hospital, San Francisco.

cartilages. There is considerable flaring of the diaphyses and the phalanges are shorter than on the left. The right hand, as compared with the left, is short and the joints are enlarged. The epiphyses apparently have been destroyed and growth arrested.

In 1935 Bennett and Blount[1] reported a very similar case in a girl aged 8 years. The x-ray pictures are almost identical.

Literature on the condition is very meager. This was a revelation, since severe frostbite must be fairly common in certain sections of the world. Is it rare or is it taken for granted? It seems apparent that not only heat and radiation but also cold may destroy epiphyses. The pathologic physiology presumably is on the basis of prolonged ischemia, possibly abetted by thrombosis of small vessels.

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Medical Progress

THE DIAGNOSIS OF SURGICAL CONDITIONS OF THE NEWBORN INFANT

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THE mortality rate in the first year of life has been considerably reduced as a result of medical progress during the past few decades. This reduction has occurred chiefly in infants over one month of age; neonatal mortality rates have been less significantly diminished. More than one-half of the deaths in the first year of life are in the first month, and one-third of these occur within the first twenty-four hours of life.

Considerable progress has been achieved in reducing mortality due to prematurity and birth injury through advances in obstetric and pediatric care. As these reductions have occurred, neonatal mortality as a result of congenital anomalies has become relatively more significant. Thus, according to the 1947 United States Summary of Vital Statistics, there are 4.6 deaths per 1,000 live births attributable to congenital anomalies, which places this group second only to prematurity as a cause of death in the neonatal period.[1] Significant opportunities for the reduction of neonatal mortality can result, therefore, from earlier diagnosis and treatment of congenital anomalies through more widespread appreciation and application of recent developments, especially those relating to surgical therapy.

Since diagnostic considerations and techniques in this age group differ significantly from those employed in older children, and certainly from many commonly utilized in adults, the recognition of these differences may be lifesaving. Some techniques useful in older age groups may contribute to an increased mortality when employed during this period of life. In order to further an understanding of the management of the newborn infant with remediable surgical conditions, this review is presented.

I. DIAGNOSIS OF ACUTE SURGICAL CONDITIONS

A. Atresias.—

1. Esophageal atresia and tracheoesophageal fistula: Although as late as 1940 the prognosis for patients with esophageal atresia alone (or associated with tracheoesophageal fistula) was poor, at the present time early diagnosis and treatment render the outlook more favorable.

Esophageal atresia alone is rare; usually it is associated with a tracheoesophageal fistula. The presence of excessive amounts of mucus in the mouth of

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a newborn infant should suggest the possibility of this anomaly. Prompt regurgitation of feedings followed by attacks of cyanosis is another characteristic of esophageal atresia. The mucus in the mouth and nasopharynx is bile-stained in 96 per cent of these cases because of the communication of the tracheoesophageal fistula with the distal esophageal segment.[2] If, during the process of gavage, the catheter meets an obstruction, one must consider the possibility of an atresia. Also, signs of atelectasis may be found upon physical examination, most commonly involving the upper portions of the lungs and more frequently the right.

Fig. 1.—Tracheo-esophageal fistula. Note the rubber catheter in the blind upper esophageal pouch. Atelectasis of right upper lobe and areas of pneumonitis in both lung fields exist. Also of interest is the gastrointestinal gas pattern present.

If one suspects this condition, a No. 8 French, soft-rubber catheter may be passed through the nasal passages into the esophagus (Fig. 1). If the catheter enters the stomach, an atresia is not present; however, the presence of the catheter in the stomach should be confirmed by fluoroscopy since the end of the catheter may curl up in the blind esophageal pouch. With the patient in the prone position and with the end of the catheter in the upper esophageal segment, under fluoroscopy one may instill 0.5 to 1.0 c.c. of Lipiodol slowly through the catheter so as to prevent the overflow of Lipiodol into the trachea with resultant aspiration pneumonitis.[3] The use of Lipiodol may be hazardous if given in

amounts larger than those suggested. The infant should be maintained in the prone position during the examination, and the oil should be removed by suction immediately upon completion of the x-ray studies. The use of barium sulfate as a contrast medium in this condition is to be condemned because of the danger of chemical pneumonitis resulting from aspiration of this substance. Umbrathor, a liquid contrast medium of thorium dioxide, has been used by us instead of Lipiodol with good results. Roentgenograms should be taken in both the anteroposterior and lateral positions.

In interpretation of the x-ray findings in this condition and in the subsequent conditions to be described, one must recall the fact that gas begins to accumulate in the stomach of a normal infant within five minutes after birth. Usually this gas is passed along into the ileum within the first two hours of life. This occurs so rapidly and so regularly that interference with this passage is useful in the diagnosis of obstruction in the newborn infant. In the newborn infant and until about one year of age, gas is usually more or less equally distributed between the small and large bowel; after about one year of age, gas in the small bowel is found less frequently. Thus, gas acts as an efficient and safe contrast medium.

An accurate differential diagnosis of the various forms of esophageal atresia and tracheoesophageal fistula may be made by roentgen examination. The presence of an intestinal pattern with a blind upper esophageal sac indicates an esophageal atresia with a fistula between the lower esophageal segment and the trachea; this picture is found in 80 to 94 per cent of these cases. If the x-ray shows an absence of intestinal gas pattern with the presence of an air-filled or Lipiodol-outlined blind upper esophageal pouch, but with no Lipiodol in the trachea, there is an esophageal atresia without associated tracheoesophageal fistula. Such findings occur in only 3 per cent of these cases. If Lipiodol enters the trachea, and if there is an absence of intestinal gas pattern, a tracheoesophageal fistula exists between the trachea and upper esophageal pouch. This occurs in approximately 1 per cent of the cases. If Lipiodol enters the trachea in the presence of an intestinal gas pattern, one may conclude that the trachea is connected to both esophageal pouches by fistulae. The incidence of this condition is also 1 per cent. A normal esophagus with Lipiodol seen in the trachea indicates a tracheoesophageal fistula without esophageal atresia.

Preoperative factors of importance include the administration of oxygen, antibacterial therapy, and constant suction of the contents of the upper esophageal pouch through a No. 10 French catheter containing multiple pin point perforations at the tip. Electrolyte and water balance must be carefully maintained.

Delay beyond twenty-four to thirty-six hours in the surgical correction of this anomaly is characterized by a marked rise in mortality.[4] The operative procedure of choice is a direct anastomosis; however, if the esophageal segments are separated by a distance of more than 1.5 cm., a multiple stage procedure is probably preferable. Twenty-four hours after the initial surgery a gastrostomy may be performed under general anesthesia, and gastrostomy feedings may be begun eight hours later. A recent report indicates excellent results when the gastros-

tomy is performed twenty-four to forty-eight hours before the anastomosis is attempted.[5] Once the diagnosis has been established, nothing should be given by mouth. Postoperatively oral feedings may be begun on the tenth postoperative day. Thirty to forty-five minutes should be allowed for each feeding to minimize the possibility of vomiting with resultant stress on the suture lines.

2. Intestinal atresia: Intestinal atresia is an uncommon congenital anomaly. Without treatment, death usually occurs within the first week of life due to severe dehydration and intestinal perforation. Although there is a high mortality rate in these infants, early diagnosis and treatment can do much to lower mortality.

The symptoms of intestinal atresia are always manifest on the first day of life.[6] Vomiting occurs and becomes progressively more frequent and severe. The vomitus is almost always bile stained. Fever may be present. The meconium stools may be small in size and dry. Abdominal distention, together with intestinal patterning, is usually an important feature. If the atresia is in the duodenum, the distention is largely confined to the epigastrium rather than diffuse in distribution; if the atresia is in the jejunum or below, generalized distention is observed. The ileum is the most frequent site of intestinal atresia.

The absence of cornified epithelial cells in the stools in the first forty-eight hours of life may be helpful in the diagnosis of congenital intestinal atresia. The basis of this test, as described by Farber,[7] is the fact that desquamated squamous epithelial cells from the skin of the fetus are present in amniotic fluid. This material is swallowed by the fetus and becomes one of the constituents of the meconium stool of the normal infant. If an atresia of the intestinal tract exists, these epithelial cells will not have passed beyond the obstruction.*

Roentgen examination is helpful in the localization of the site of obstruction. The gas which is already present in the intestinal tract serves as the best contrast medium.[8] Thus, a dilated duodenum or other loop of intestine may be seen. The use of barium as a contrast medium administered orally or rectally in the diagnosis of this condition is contraindicated because of the danger of vomiting, aspiration, or perforation, as well as the hazard of causing further obstruction by inspissation in the intestinal tract. Roentgenograms should be taken in both the upright and the inverted position thus showing the extent of the gas-filled intestinal loops.

Preoperatively, decompression by means of Wangensteen suction is of utmost importance. Decompression must be accomplished within three or four days or perforation will occur.[9] Increasing the oxygen concentration of the inspired air by placing the infant in an oxygen tent may also aid decompression.

Primary anastomosis is the surgical procedure of choice in intestinal atresia. Examination of the entire intestinal tract is indicated at the time of surgery because of the possibility of multiple atresias.

*The technique for this test is as follows: Make a thin smear of the center of a meconium stool on a glass slide. Wash for one minute with ether for fat extraction; dry; stain with Sterling's gentian violet for one minute; decolorize with acid alcohol. Only the cornified epithelial cells will retain the dye.

Enterostomy in general is undesirable in the treatment of intestinal anomalies in infants because of the difficulty of maintaining adequate hydration in the face of large fluid loss through the enterostomy.

Intestinal stenosis with obstruction during the first week of life occurs most frequently in the duodenum and cannot be differentiated clinically from atresia. If obstruction develops after birth, however, one might find cornified epithelial cells in the stool. Primary anastomosis is indicated with excision of the stenotic area. Dilatation is not satisfactory treatment.

3. *Imperforate anus:* Seventy-five per cent of patients with anorectal malformations develop acute obstructions following birth, and are, therefore, brought to the attention of the physician in the first few days of life because of one of the following: (1) absence of an anal opening, (2) failure to pass stools, or (3) passage of meconium through an abnormal outlet. There are three types of rectal anomalies in general. The most common consists of an imperforate anus with a rectal pouch ending blindly some distance above. The second type is that in which the proximal rectal pouch ends blindly in the hollow of the sacrum with a normal anus and distal rectal pouch. The least common form is an imperforate anus with an obstruction due to a persistent membrane. These anomalies are commonly accompanied by fistulae; in one series, fifty-five per cent had fistulae between the rectum and genitourinary tract or the perineum.[10]

In addition to the absence of meconium stools, one observes abdominal distention, emesis, and other symptoms of obstruction within twenty-four to thirty-six hours. Other signs of lower bowel obstruction include intestinal patterning, borborygmi, tympanites, dehydration, and finally, respiratory and circulatory collapse. If the infant is observed within the first twenty-four hours of life, these signs of intestinal obstruction are rarely found. Examination will reveal a dimpling and puckering of the skin in the anal area in the most commonly seen form of this condition. In the type due to a persistent membrane there will be a dark discoloration of the skin at the anal dimple, which is caused by the presence of underlying meconium. When the infant cries, this area bulges. In the third group rectal examination will reveal a blind pouch.

Roentgen examination by the Wangensteen-Rice method will help to determine the position of the blind rectal pouch.[11] The infant is held with his head down and with a lead marker in place over the skin at the anal site. Anteroposterior and lateral films should be taken. The gas which is present in the colon rises and outlines the blind rectal pouch. This procedure when employed by the end of the first day may be very helpful. Examinations performed prior to this time may be misleading because insufficient time may have elapsed to permit air to reach the distal portion of the large bowel. Surgical therapy of this condition is dependent upon the anatomical relationship of the rectum to the anal site and upon the surgical difficulties which may involve closure of anomalous fistulae.

B. Miscellaneous.—

1. Malrotation of the intestine: In about one-half of the reported cases of malrotation of the intestine, symptoms become manifest within the first three weeks of life. Findings are usually those associated with high intestinal obstruc-

tion and are due to external pressure on the second or third parts of the duodenum. Persistent vomiting, usually bile-stained, occurs. Bowel movements usually occur since the obstruction is only partial. Abdominal distention with peristaltic waves progressing downward on the right side of the epigastrium may be seen. Fever may be noted because of dehydration. With a continued rise in temperature, the occurrence of volvulus and infarction may be suspected. In infants under one week of age this clinical picture may simulate intestinal atresia or intestinal stenosis with obstruction. In either event, an exploratory laparotomy is indicated.

A scout film of the abdomen usually shows a gas-filled, dilated stomach and duodenum if vomiting has not emptied both the stomach and duodenum. The absence of distended stomach and duodenal shadows does not necessarily rule out the presence of this anomaly. In most cases it is wiser not to use contrast media other than the air which is already present in the bowel, since the usual x-rays and clinical picture give evidence of intestinal obstruction. It is best to proceed with surgical therapy without delay.

Certain principles have been found to be most effective in the surgical treatment of this condition.[12] A long right paramedian incision should be made to allow adequate exposure. Inspection of abdominal contents determines the procedure to be followed. If the cecum is found in the right upper quadrant with the ascending and transverse colon visible, the posterior parietal peritoneum to the right of the cecum should be incised and the cecum transferred to the left, thus taking pressure off of the duodenum. No attempt should be made to restore the cecum to its normal anatomical position since such a procedure does not relieve the obstruction. Also, no short-circuiting anastomosis is indicated. If discolored small intestine is the presenting part upon opening the abdomen, and the ascending colon is not visible, a volvulus should be suspected. In the treatment of this condition, the entire midgut must be withdrawn from the abdominal cavity so that the volvulus may be found. To reduce the volvulus, the mass usually must be turned in a counterclockwise fashion. After this is done the cecum and ascending colon should be freed in the right lower quadrant and transferred to the left. Mortality is high if this is not done.

2. Diaphragmatic hernia: Before 1931, 75 per cent of patients with congenital diaphragmatic hernia died before the age of one month.[13] Of diaphragmatic hernias occurring in the neonatal period, 85 to 90 per cent can be cured by surgical procedures at the present time. This marked reduction in mortality is due to early diagnosis with immediate surgery, to improved surgical technique, and to better pre- and postoperative care. One cannot employ the same surgical procedures found helpful in the adult for the treatment of this condition in the newborn infant.

The diagnosis of congenital diaphragmatic hernia must be considered in newborn infants who present the symptoms of cyanosis, dyspnea, or vomiting. The cyanosis may be present at birth or may occur only with feeding or crying; it may sometimes be relieved by turning the infant so that the side with the hernia is downward, thus allowing the mediastinum to fall toward the affected side and allowing better expansion of the other lung. Emesis may be occasional or may follow most of the feedings.

Pulse and respiratory rates are increased. Respiratory excursions on the affected side are decreased. Percussion of the involved side may reveal dullness or tympany. The heart is displaced to the opposite side; breath sounds are distant or absent, and bowel sounds may be heard in the chest. If most of the gastrointestinal tract is in the thorax, the abdomen may appear scaphoid.

Roentgenograms and fluoroscopy will confirm the diagnosis and will permit the identification of the herniating structures. The use of barium as a contrast medium is contraindicated except in the presence of an esophageal hiatus hernia, since the intestinal gas will usually provide the information needed. In esophageal hiatus hernia, one must be able to visualize the length of the esophagus and the size of the diaphragmatic hernia to determine the indications for surgery.

Immediate surgery is mandatory in all except the occasional case with a small esophageal hernia. Waiting until the infant is "older and stronger" will result in a high mortality rate, since the infant withstands major surgery better in the first forty-eight hours of life than at the age of seven to ten days.[14] Also of advantage is the fact that during the first forty-eight hours of life the intestine usually has not become distended, and this may make the difference between being able or not being able to replace the intestines in the abdominal cavity.

The anesthetic of choice is cyclopropane, since this agent may be given with a high concentration of oxygen.[15] An abdominal approach should be used as contrasted to the usual thoracic approach in adults. A thoracic approach in infants does not facilitate a reduction of the hernia, because the abdominal cavity is often too small to contain all of the viscera. Also mechanically it is easier to pull abdominal viscera out of the chest from below than to push them down from above. This can be accomplished in infants because it is very rare for any adhesions to exist between abdominal and pleural contents.[16] After entering the peritoneal cavity, a rubber catheter should be placed through the hernial ring into the thorax or the intestines will be sucked back into the thorax as fast as they are withdrawn.

The closure of the abdominal wall also differs from the usual procedure in adults. Since the abdomen never contained all of its viscera and is, therefore, poorly developed, many times it will be impossible to close the abdominal wall in one stage. In such cases the skin should be undercut and allowed to slide; the subcutaneous fascia and skin may then be closed. Secondary repair may be performed five or six days later when the abdominal wall has stretched. The two-stage procedure has contributed to the lowered mortality in the correction of this anomaly.

Indications for surgical treatment of esophageal hiatus hernia include evidences of gastric or intestinal obstruction at the hernial ring or severe bleeding from a mucosal ulceration caused by constriction of the stomach at the hernial ring. A thoracic transpleural approach in the repair of the hiatus hernia is to be preferred if much dissection of the esophagus is anticipated.

3. Omphalocele: An omphalocele represents the herniation of the abdominal contents into an abnormal saclike umbilical cord, so that these abdominal contents are covered by peritoneum and amniotic membrane only. During the first

twelve to eighteen hours, these infants usually evidence no discomfort and no respiratory difficulty or signs of intestinal obstruction. The diagnosis is obvious upon inspection of the infant. This condition calls for immediate surgery. The mortality rate increases in direct proportion to the delay in surgical correction.[17] This defect may be closed either in one or two stages, depending upon the size of the omphalocele and the ease with which the viscera may be replaced within the abdominal cavity.[18] If the closure would result in respiratory or circulatory embarrassment, a two-stage procedure should be done in which the peritoneum and posterior rectus fascia are not approximated, and only the subcutaneous tissue and skin are brought together. A secondary closure may be done in the succeeding weeks after the muscle and fascia have stretched. These infants should be observed for signs of circulatory and respiratory difficulty and for evidence of intestinal obstruction postoperatively.

4. Meconium ileus: Meconium ileus in the newborn infant manifests itself as severe intestinal obstruction with early onset of emesis which is usually bile stained. A plain film of the abdomen may demonstrate the extent of obstruction. Neuhauser[18a] has observed minute bubbles of gas mixed with the thick meconium on the plain film in 40 per cent of cases. The meconium stools are ropy. Whenever this condition exists, one should consider the possibility of fibrosis of the pancreas.[19, 20] Prompt exploration with an attempt to dislodge the thick, tenacious meconium is probably desirable, although the administration of pancreatic enzymes enterally and by enema has proved helpful in relieving obstruction in some cases. The prognosis generally is very poor when this condition is observed as a manifestation of fibrosis of the pancreas so early in life.

5. Functional intestinal obstruction: The existence of functional intestinal obstruction as a clinical entity has been emphasized recently.[21] It becomes manifest within the first few days or weeks of life. Symptoms are those of intestinal obstruction with emesis. Constipation and abdominal distention with audible and visible peristalsis usually occur. If the distention becomes extreme, the picture of paralytic ileus ensues. Rectal examination usually reveals a fecal mass in the rectum and the presence of a tight anal sphincter. The x-ray reveals only the usual findings of intestinal obstruction except in protracted cases in which enlargement of the colon may be present. It is impossible to establish a definite preoperative diagnosis of this condition, except for the fact that a familial incidence has been described which may make one suspect this diagnosis. Also the presence of fecal impactions (which are not always demonstrable prior to surgery) should raise the question of some disturbance of intestinal motility. Fecal impactions in the newborn child, therefore, have a significance different from those in older age groups. The treatment of choice is believed to be exploratory laparotomy. In those patients who are explored because of evidences of intestinal obstruction and in whom no mechanical cause for the obstruction is found, the possibility of functional intestinal obstruction must be considered; therefore, the surgeon should not close the abdomen without considering the need for an enterostomy at the lowest level of normal intestinal motility. Zuelzer and Wilson[21] have reported a good correlation between the levels of obstruction as determined during surgery or at autopsy, and the levels in which absence of

the myenteric plexus occurred upon histological examination. The number of cases in which this condition has been recognized and treatment instituted has been small. The determination of the most effective therapy must, therefore, await further study.

6. Appendicitis: Although not a congenital anomaly, appendicitis in the newborn period may present diagnostic confusion with gastrointestinal anomalies. At least thirty cases have been reported in infants under one month of age.[22] There is a greater tendency for the appendix to rupture, resulting in generalized peritonitis during early infancy. Symptoms include restlessness, irritability, frequent crying, abdominal distention, and inability to sleep. Emesis may occur, but pain is invariably present. It may be impossible to make out any localized tenderness upon abdominal examination. Rectal examination may reveal an area of tenderness or a mass. The diagnosis of appendicitis should be considered in any infant presenting the above signs and symptoms, and it will be only through cognizance of the possible occurrence of this condition in the newborn period that early diagnosis and treatment can be accomplished.

7. Peptic Ulcer: Although this condition is rare, it has been found in both premature and stillborn infants. The ulcers run a more acute course in infants than in adults. Their incidence is actually greater in infancy than in childhood. In the majority of cases this condition is asymptomatic. The occurrence of repeated gastric upsets, hemorrhage, or evidence of perforation should make one consider this diagnosis. The bland diet of infancy is usually sufficient for treatment; however, if bleeding occurs, blood transfusion is, of course, indicated. With perforation, a high mortality exists. The only hope is that of early surgical treatment. This treatment differs from that in adults in that the perforation should be plugged by laying a piece of omental fat over the opening and by tying three or four sutures over it placed at opposite margins of the perforation. Plication or excision of the ulcer are not recommended since contracure and obstruction may result.

8. Meckel's diverticulum: The sudden painless passage of a bloody stool in a previously asymptomatic infant, with an increase in pulse rate, and the appearance of marked pallor, lethargy, and eventual collapse, suggests Meckel's diverticulum with hemorrhage. The amount of blood lost is massive in contrast to the bleeding from rectal polyps or anal fissures. Intussusception at the site of the diverticulum is accompanied by evidences of pain and by the presence of a palpable mass. Intestinal obstruction may develop as a result of volvulus about the band between the diverticulum and the abdominal wall. Roentgen examination contributes nothing toward the diagnosis of Meckel's diverticulum specifically. It may present symptoms at any age, but complications usually make their appearance early in life. In the presence of massive blood loss, transfusion and immediate surgery are indicated.[23]

9. Meckel's diverticulitis: This condition may occur with or without perforation. If untreated, it may progress to perforation with a spreading peritonitis. The differentiation of this condition from appendicitis is difficult, but the treatment of both is surgical.

10. Intussusception: Although rarely seen in the newborn period, intussusception is one of the most important surgical emergencies in infancy. This condition must be recognized within the first twenty-four hours after onset in order to insure a favorable prognosis. In contrast to the situation in older children and adults, a local cause for the intussusception is found in few instances. This condition is characterized by the occurrence of recurrent, colicky, abdominal pain causing the infant to cry, to flex his legs, and to manifest a grunting type of respiration. These episodes last ten to fifteen seconds, after which time the infant may appear normal. Early and repeated emesis may occur. The passage of bloody stools occurs in about 85 per cent of these cases, but this is a relatively late occurrence usually not observed until twelve to fourteen hours after the onset.

Abdominal palpation will usually reveal a rather firm, nontender mass. There may be a feeling of emptiness in the right lower quadrant because of the invagination of the cecum into the colon. If the abdomen cannot be satisfactorily palpated due to the crying of the infant, and if further confirmatory findings are desired, the infant may be sedated with 0.1 grain of Seconal per pound of body weight given rectally. Upon rectal examination one may feel a mass representing the advancing point of the intussusception; blood may be present on the tip of the examining finger.

Once a diagnosis is established, surgery is the treatment to be instituted. Reduction by barium enema under fluoroscopic examination is not relied upon by most surgeons for complete reduction, although such reductions have recently been advocated again. It is well to visualize the bowel to determine its state of viability. An important surgical principle to be followed in these cases is that no more than is absolutely necessary should be done if the bowel is viable.[24] Any opening into the bowel for the removal of polyps or other possible causes should be deferred to a second procedure which may be performed ten to fourteen days later. If a resection must be done, a Mikulicz procedure is preferred by most surgeons rather than a primary anastomosis. At the present time, attempts to prevent recurrences through surgical procedures are not recommended, since recurrences of intussusception develop only in about 2 per cent of the cases reported. Since the recurrence may not develop in the same location as the original intussusception, surgical attempts at prevention may meet with failure, thus increasing operative mortality.

11. Duplications of the alimentary tract: A duplication of the gastrointestinal tract is a hollow structure with a smooth-muscle coat lined by mucous membrane and intimately attached to some part of the gastrointestinal tract. It is called a duplication because it is a replica of some part of the intestinal tract, although not necessarily of that part to which it is contiguous.

Signs of obstruction may be present in these cases with epigastric fullness, visible peristalsis, emesis, and dehydration. There may be severe, repeated hemorrhage from the lower intestinal tract. A colicky type of pain may be present. A rounded, smooth, and nontender mass may be palpated.[25] Anteroposterior and lateral films without the use of contrast media other than the gas already present in the gastrointestinal tract will provide additional information.

Surgical treatment consists of resection of both the duplication and the adjacent gut and re-establishment of intestinal continuity by a side-to-side anastomosis. Naturally, the presence of alimentary duplications in certain locations precludes such management.

12. Cysts of the umbilical cord: In this condition there is an accumulation of Wharton's jelly within the umbilical cord. If such a cyst appears at the base of the umbilical cord, no space exists between the cyst and the abdominal wall; therefore, the cord must be tied distal to the cyst. The cyst should be removed surgically from the abdominal wall within the first twenty-four hours of life because of the danger of infection.

13. Abscess of the abdominal wall: An abscess of the abdominal wall may be the result of an omphalitis. Gentle pressure above or below the umbilicus will express pus which has accumulated along the falciform ligament or the hypogastric arteries. A probe may be passed through the umbilical opening into the abscess tract along the path of the hypogastric arteries. The full thickness of the abdominal wall anterior to the sinus tract should be laid open. The use of antibacterial agents is indicated because of the great danger of bacteremia.

II. URGENT SURGICAL CONDITIONS

A. Pyloric stenosis.—

Pyloric stenosis is the most common condition requiring surgery in the first month of life.[26] Symptoms are those due to high obstruction. These include projectile vomiting which usually begins during the second week of life. (In a few infants included in a series of twenty-seven consecutive cases which we recently studied, vomiting had begun on the first day of life.) The emesis contains no bile. At first regurgitation may be the only complaint, and this only after occasional feedings; later the vomiting is projectile and occurs after all feedings. The infant is hungry and will take feedings eagerly. Stools become infrequent and small in amount. Usually there is a failure to gain weight. Gastric peristaltic waves may be seen passing from left to right in the epigastric region. In approximately 95 per cent of these cases, careful palpation will reveal the pyloric tumor in the right upper quadrant. This tumor can be felt best immediately after the infant has vomited while the abdomen is relaxed. The examiner should stand on the left side of the infant and should use only one finger in the palpation. This tumor is more frequently felt in the area between the right rectus muscle and the costal margin. In untreated cases dehydration may become severe. Although pyloric stenosis is most frequent in male infants, it is not uncommon in female infants. Use of barium and fluoroscopy is not essential for the diagnosis of this condition. Treatment of choice is the Fredet-Ramstedt operation after preoperative establishment of fluid and electrolyte balance.

Attention has recently been called to two conditions which might be confused with pyloric stenosis. The first, brachyesophagus, is a congenital malformation consisting of an abnormally short esophagus with the cardia of the stomach in the midthorax.[27, 27a] Emesis is the chief symptom and may appear immediately

after birth or in the first weeks of life; however, it may not occur until solid food is taken. Daily emesis during meals occurs. X-rays, after swallowed barium sulfate or Umbrathor, taken in the vertical, horizontal, and Trendelenburg positions will reveal the diagnosis. The treatment at present is symptomatic and a possible complication is that of esophageal ulcer.

In an infant with persistent emesis but without any of the other signs found in pyloric stenosis, chalasia of the esophagus must be considered. In this condition an upper gastrointestinal series with fluoroscopy will show a continuous relaxation of the gastric cardia allowing frequent regurgitation. With the use of thickened feedings and with the infant maintained in Fowler's position after feedings, the vomiting can be prevented. Thus a differentiation from pyloric stenosis may be made.[28]

B. Stenoses.—

1. Intestinal stenosis: This condition is most often found in the duodenum. As previously indicated, it is usually characterized by the development of an obstruction at that site during the first week of life, thus constituting an acute surgical condition. In the absence of total obstruction, however, infants with this anomaly may continue for many weeks with such vague complaints as "feeding difficulties," that is, only occasional emesis and a slow weight gain. In these infants a gastrointestinal x-ray series using Umbrathor as the contrast medium may be diagnostic. Treatment is the same as previously noted for intestinal stenosis with obstruction.

2. Stenosis of rectum with megacolon: In patients with congenital megacolon, Neuhauser and Swenson[29] have reported the finding of a stenotic area in the rectum just distal to the dilated portion of the bowel. This can be demonstrated by inserting a catheter above the stenosis and by slowly instilling a thin mixture of barium sulfate through the catheter. If this stenotic area is then resected, the dilated proximal segment of colon has been found to return to its normal size. Also the colon becomes functionally normal with resultant passage of normal stools. In order to remove the stenotic area and still preserve the anal sphincter, a new method of resection has been devised by Swenson.[29a] Results have been very satisfactory in a reported series of twelve patients.

C. Congenital Biliary Atresia.—

In this condition jaundice may be present at birth or appear shortly thereafter, although often it is not noticed until the age of 2 to 3 weeks. The jaundice is persistent in nature once it has appeared. These infants are usually in good general condition in the first 2 or 3 months of life. An enlarged liver and spleen may be present. The stools are clay-colored or white even before the appearance of recognizable jaundice; however, the intestinal mucosa may impart a faint yellowish tint to the stool as the jaundice increases. The urine is also dark and gives a positive test for bile. The prothrombin time is usually normal.

This condition must be differentiated from several other causes of jaundice in this age period. Physiologic jaundice of the newborn infant is usually differentiated by the decrease in intensity of the jaundice noted between the second

and fourth week. The color of the stools and urine is normal. Erythroblastosis fetalis may be characterized by a golden-colored vernix caseosa and a large placenta. Other findings of importance include blood group incompatibility on typing of the infant and mother, antibody titers, anemia, history of previous pregnancies, and an increased number of nucleated red blood cells in peripheral blood. It may be well to point out that intrahepatic obstruction may occur during the course of severe erythroblastosis fetalis resulting in the passage of acholic stools; this phase usually clears if the infant survives, and the stools regain their normal color as the intrahepatic obstruction clears. Sepsis of the newborn infant may be associated with jaundice, but this condition may be differentiated by the toxic appearance of the infant, the presence of fever, positive blood culture, and the presence of stools of normal color. Congenital syphilis is characterized by positive serology in the mother and infant, osteochondritis, snuffles, and rash. Infectious hepatitis when it presents the symptom of jaundice is difficult to differentiate; liver function tests and the course of the disease[30] may be of help in the diagnosis.

It is usually advisable to postpone surgical correction until the fourth week of life. Approximately 15 to 20 per cent of these atresias can be corrected; therefore, all of these infants merit exploratory laparotomy. Cirrhosis of the liver is not a contraindication to surgery since the liver has great regenerative powers.

DISCUSSION

Throughout this paper, emphasis has been placed upon those procedures which lead to a lowered mortality in those conditions amenable to surgery in the newborn period. Prompt recognition and prompt surgical intervention have been stressed. In addition, however, the mortality experienced in the diagnosis and in the surgical correction may be favorably influenced by attention to certain details in diagnostic methods and in proper pre- and postoperative care.

One such important detail is the use of the proper contrast medium in roentgenograph studies. Umbrathor and the iodized materials are relatively safer contrast media to use when need for contrast study arises. Umbrathor is a liquid medium and is less likely to cause obstruction than barium. Its radioactivity is not a contraindication to its use in the gastrointestinal tract where it is not absorbed.[31, 32]

Another factor of significance is the type of anesthesia.[33] In most instances, general anesthesia is preferred for satisfactory abdominal relaxation. The simple procedure of keeping the infant warm during surgery by use of a wrapped hot water bottle placed under him should not be overlooked.

One of the most important aspects of pre- and postoperative care is the careful regulation of the electrolyte, fluid, and nutritional balance in these infants. Special caution should be observed in determining the amount of saline to be administered to newborn infants, since kidney function in this age group is relatively immature. The administration of excessive amounts of sodium may lead to edema. Since space does not permit a full discussion of fluid, nutritional, and electrolyte balance, the reader is referred to an excellent discussion of this

subject by Butler and Talbot.[34] Another consideration in this age period is the presence of a physiological hypoprothrombinemia, and in such cases vitamin K should be administered.

Blood transfusions or plasma should be given as indicated by the red blood count, hematocrit, and plasma protein level. The rate of administration of the blood should be slow in debilitated infants to prevent circulatory embarrassment. Because of possible blood loss at the time of surgery or the development of shock, a cannula should be inserted into a vein prior to surgery for immediate use in event of emergency need for fluid administration. Fluids are often administered during surgery.

In those conditions in which decompression of the gastrointestinal tract is desired, the simple procedure of passing a Levine tube into the stomach and connecting the tube to a source of gentle suction is expedient in reducing distention. With decompression, respiratory exchange is aided by permitting greater diaphragmatic excursion, thus increasing the vital capacity of the infant. The use of high oxygen concentrations in a tent is also helpful in diminishing the intestinal distention.

SUMMARY

1. The importance of early recognition and of immediate treatment of surgical conditions in the newborn infant is stressed. The mortality in a given case is directly related to the promptness of diagnosis and proper surgical treatment.

2. Diagnostic techniques employed in the newborn period differ from those in older age groups.

3. The gas normally present in the gastrointestinal tract of the newborn infant serves as a safe and effective contrast medium in roentgen studies. In general, the use of barium sulfate is to be condemned. The cautious use of Lipiodal is permissible in certain selected cases. Umbrathor is discussed as an expedient contrast medium.

4. Surgical procedures customarily indicated at other age periods may actually contribute to the mortality rate in this age period.

5. A review of surgical conditions in the newborn period is presented.

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Psychologic Aspects of Pediatrics

SIXTY YEARS OF CHILD TRAINING PRACTICES

Revolution in the Nursery

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THE past two decades have witnessed a revolution in child training practices in America which has been tremendous in its scope and far-reaching in its effects. From an era where the mother was taught that the child must have his physical wants cared for and then be left alone, must be fed on a rigid schedule, must learn to cry it out, must be toilet trained early and must not be spoiled by attention, we have come to a time when exactly the opposite advice is advocated. Today the mother is advised to feed the baby when he's hungry, to delay toilet training until he's ready for it, to see that the baby gets a reasonable amount of cuddling and mothering, to let the baby initiate the weaning process. And just as a mother of 1930 was taught that the popular doctrine of 1930 would produce the right kind of child, so the mother of today is assured that if she weans and toilet trains and cuddles in the approved fashion, her child will have a well-adjusted personality.

Yet there appears to be considerable question as to whether the new doctrine is any sounder than the old. Orlansky[1] examined experimental and semiexperimental investigations carried on in Western culture, as well as evidence from anthropologic studies on the relationship between infant disciplines and personality. Studies on breast feeding versus bottle feeding, self-demand versus scheduled feeding, weaning, thumb-sucking, mothering, sphincter training, and early childhood conditioning were carefully reviewed. From the extensive evidence in the literature, he arrived at a definite but negative conclusion in regard to the effect of certain features of infant care upon personality. It would appear that the assertion that breast-fed babies are invariably better off than bottle-fed babies remains unproved; that the connection between self-demand or scheduled feeding and a secure, well-adjusted personality remains to be shown; that "mothering" or not "mothering," early toilet training or late may or may not affect personality.

If, then, there is no scientific justification for the revolutionary changes in child rearing practices, the question might be raised as to why such changes come about. From Orlansky's evidence it would seem that the reasons for the revolution lie outside the realm of scientific fact. In order to get some perspective on the changes in practice, perhaps it might be helpful to go back in history to see what has been advocated with regard to the rearing of children in the past. For this purpose, approximately sixty years of child-training practices as advocated in three popular women's magazines has been studied. These

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magazines are: *Ladies Home Journal*, *Woman's Home Companion*, and *Good Housekeeping*. Beginning with 1890, every issue of each magazine for the first year in each decade has been scanned and an analysis made of the articles dealing with child-training practices. There have been three exceptions to this: the *Ladies Home Journal* for the year 1890-1891 was not available, and the 1891-1892 volume was substituted. The *Woman's Home Companion* for the entire decade, 1890-1900, could not be located and had to be omitted entirely. The 1921 volume was substituted for the 1920 volume of that same magazine. The year 1948-1949 was selected for analyzing the most recent examples of child-training practices.

PURPOSE AND PROCEDURES

I had two purposes in mind in analyzing the articles on child rearing found in the magazines mentioned above. One of these was to examine the content of each article to see changes in the kinds of topics dealt with over the past sixty years. The second purpose was to see what was being advocated as good child-training procedures during each period studied. An attempt was also made to relate these changes to social and intellectual trends of the times. Two checklists were prepared for use in collecting data. One of these, based upon a preliminary examination of some of the periodicals, included the following list of topics:

1. *Physical Development.*
   Included here were all topics dealing with physical and motor development, such as formulas, fresh air, sunshine, vitamins, and the like.
2. *Specific Behavior Problems.*
   This category included articles dealing with one or more behavior problems such as thumb-sucking, manners, feeding problems after infancy, disobedience, and the like.
3. *Infant Disciplines.*
   Here were grouped those articles dealing with scheduling of infant feeding, weaning, toilet training, cuddling, etc.
4. *Character and Personality Development.*
   Problems relating to the development of a good character, including articles on developing honesty, thrift, etc., were listed here, as well as those articles dealing with good personality adjustment.
5. *Developmental Stages.*
   These were articles dealing with a particular stage of development, as for example, adolescence. Also included here were any articles which attempted to describe behavior at various stages of development.
6. *Sex Education.*
7. *The Place of Father.*
8. *Miscellaneous.*

It was recognized that in any list of topics there would be a good deal of overlapping. This was partly because some articles dealt with more than one of the topics listed. A writer, for example, might have touched upon behavior problems, physical development, and character training all in one article. In such cases a tally was placed for each topic discussed. This meant that the

number of topics listed would be greater than the number of articles read. Totals by topic as well as by article are included in the tables. Where percentages are shown, the total number of topics was used as a base.

A more difficult problem, however, was the kind of overlapping that came because of the relatedness of the topics. Infant Disciplines might have been included under Physical Development, for example, or under Character and Personality Development in some cases. Where an article dealing with only one topic might conceivably be listed under several headings, the decision regarding its placement rested upon the judgment of the analyzer in terms of the emphasis implied in the article.

The reader may question why The Place of Father is included as a topic and not a similar one for mother. However, it must be remembered that the magazines studied were written for women and would as a matter of course emphasize the place of mother.

A second checklist prepared for the purpose of recording what was advocated as good child-training practice for each decade follows:

1. *Guiding Character or Personality Development.*
   a. Discipline (Reward and/or punish)
   b. Provide a good home influence. (Articles having to do with the influence of mother, early childhood training, and the like were included here.)
   c. Ignore undesirable behavior.
   d. Look for the cause and plan accordingly.
   e. Invoke divine aid.
   f. Feed properly.
   g. Miscellaneous.
2. *Infant Disciplines.*
   a. Tightly schedule, cry it out. (This included all procedures implying a rigid attitude toward child training.)
   b. Loosely schedule.
   c. Self-regulate, "mother." (Here were included procedures of a *permissive* nature in child training.)

It was recognized that no checklist would be adequate to give the feeling of many of the articles on child-rearing practices. Therefore, it was decided that quotations from or a summary of each article should be made so that the flavor of each article might not be lost.

RESULTS

Turning first to 1890, one is impressed by the tremendous interest in problems of child rearing shown by the mother of that time. Despite the fact that the 1890-1891 volume of one of the magazines was not available for study, a total of fifty-three articles appeared in the other two volumes dealing with child-rearing practices. If one were to assume that the third magazine would yield as many articles as did the other two, then the total number of articles for the year 1890-1891 would have been seventy-nine. This compares with a total of fifty-nine articles for the year 1940 for all three magazines and a total of sixty-six articles for the year 1948-1949. Part of the interest in child train-

ing came from the fact that adult education in general and women's clubs in particular were flourishing. In 1889 the General Federation of Woman's Clubs had been formed and hundreds of thousands of women members were devoting part of their club time to the problems of child rearing.

The data in Table I show that in 1890, like most of the other periods studied, the primary interest was in physical development (discussed in 38 per cent of the articles), with character development running a close second (discussed in 35 per cent of the articles). During this period it was fairly easy to make a distinction between character and personality development. The mother of 1890 was chiefly concerned with the development of good *moral* character; the term "well-adjusted personality" was unknown in the literature of her day. And not such vaguely defined products as "well adjusted" and "secure" children were sought but rather child-training practices were designed to produce children who would exemplify the Victorian ideals of courtesy, honesty, orderliness, industriousness, and generosity; character, not personality, was the focal point.

TABLE I. PERCENTAGE OF TOPICS DEALING WITH VARIOUS ASPECTS OF CHILD TRAINING AS THEY APPEARED IN THREE WOMEN'S MAGAZINES ANALYZED IN TEN-YEAR INTERVALS FOR 1890-1948

	% 1890	% 1900	% 1910	% 1920	% 1930	% 1940	% 1948
Physical development	38	19	24	30	49	22	27
Specific behavior problems	11	20	13	22	15	18	10
Infant disciplines	11	10	17	8	12	15	12
Character and/or personality development	35	31	39	3	24	23	21
Developmental stages	1	3	7	1	5	10	9
Sex education	0	6	0	1	1	4	0
The place of Father	0	4	3	1	5	0	2
Miscellaneous	3	4	10	31	3	6	17
Total topics	63	95	75	82	65	76	80
Total articles	53	78	62	65	49	59	66

A glance at Table II reveals the procedure by which good character was to be developed, namely, through the influence of the home. Sixty-one per cent of the articles published during this year emphasized the importance of a good *Christian* atmosphere in the home with Mother seen as the crucial person in the formation of good character. "The very atmosphere of their home shapes and molds their character, even when there is no formal teaching whatever,"[2] wrote one authority and since the key person in establishing the right atmosphere at home was Mother, it followed that she should enjoy an exalted position in the household. As one writer put it, "the roots of all pure love, of piety and honor must spring from this home. . . no honor can be higher than to know that she has built such a home. . . to preside there with such skill that husband and children will rise up and call her blessed is nobler than to rule an empire. . ."[3]

I could go on with quotation after quotation emphasizing the exalted position of the mother and her importance in setting the stage for proper character development. Rather than continuing with quotes, however, it might be more pertinent to look at some of the reasons for the importance assigned to motherhood.

TABLE II. PERCENTAGE OF METHODS RECOMMENDED FOR TWO ASPECTS OF CHILD TRAINING AS THEY APPEARED IN THREE WOMEN'S MAGAZINES ANALYZED IN 10-YEAR INTERVALS FOR 1890-1948

	% 1890	% 1900	% 1910	% 1920	% 1930	% 1940	% 1948
I. Guiding Character or Personality Development							
Discipline (reward and/or punish)	18	14	34	34	38	28	2
Provide a good home influence	61	53	30	12	14	5	3
Ignore undesirable behavior	12	5	9	0	12	18	4
Look for cause and plan accordingly	0	0	0	1	14	48	84
Invoke divine aid	15	20	15	0	0	0	0
Feed properly	0	0	0	50	0	0	0
Miscellaneous	4	5	12	3	21	2	8
II. Infant Disciplines							
Tightly schedule, cry it out	0	22	77	100	75	33	0
Loosely schedule	100	78	23	0	0	0	0
Self-regulate, "mother"	0	0	0	0	25	66	100

Part of the reason for emphasizing the place of Mother in the home was because it was generally believed that good character was developed by imitation. In all of the literature of 1890, there was little talk of good home atmosphere as a necessary element of mental health of the child. It was rather that the mother should be good, honest, cheerful, and orderly because whatever kind of behavior she portrayed, the child would imitate. The earlier work of Darwin had emphasized that man was a product of forces that work upon him. Therefore, not formal schooling, but informal teaching by the person closest to the child was of fundamental importance. Everything that Mother did was seen as having a lasting effect upon her children, and motherhood was exalted as never before. Walt Whitman in poetry and Whistler on canvas testified to this same exaltation of motherhood.[4]

It might be argued that emphasizing the importance of mother was merely a way of building up her role in the home as a means of keeping her there at a time when more and more women were going to work outside the home. Yet an examination of the social scene of 1890 will reveal certain forces in operation which belie that argument. As historians have pointed out, 1890 represented the triumph of business enterprise. This had several implications for family life. For one thing, as Father lived more and more of his waking hours outside the home, Mother took over the management of the children so that she actually *was* more important than she had been. Furthermore, the business world which Father had entered was sordid; the traditional morals which had operated in a face-to-face society did not hold when social distance was increased. To offset this sordidness, women were put on a pedestal. Maternal love and affection were emphasized as a possible check on the evils of materialism. A romantic and sentimental picture of women in general was built up and mothers in particular basked in this new glory.[5]

While later generations might poke fun at the mauve decade with its romantic and sentimental emphasis, one thing is clear. Mothers occupied a

position of importance which they have never since recovered. This was the day when Mother knew best; there was no book, no scientific authority to shake her maternal self-confidence, and she could tend her flock with the calm assurance that her "instincts" were right.

It is interesting to note, too, in connection with this first period studied, that the articles on Infant Disciplines were not discussed in the same context as they are today. All of the articles dealing with this topic advocated a loosely scheduled procedure. In an article on infant feeding rather casual mention might be made that baby should be fed every two hours. Or an author might state that food could be given between feedings if the baby seemed hungry. Actually, feeding procedures did not constitute a crucial problem for the 1890 mother and were not seen as related to character and personality development.

For the most part, the same trend in child-rearing practices continued at the turn of the century. Character development was discussed in 31 per cent of the articles in 1900 with about one-half of these emphasizing a good home influence as the means to that end. Again, as in 1890, Mother and mother-love were all-important elements in child rearing. "Love, petting, and indulgence will not hurt a child if at the same time he is taught to be unselfish and obedient. Love is the mighty solvent," wrote one editor.[6] Another writer outlined her plan for treating a boy who was labelled lazy, careless, and good-for-nothing, "I thought I would try to win him with love alone, and never strike him. . . Mothers who have trouble with their children, bring them up the Christian way. . . with a loving and tender heart, and you will surely succeed. . ."[7]

A delightful verse, dating from a still earlier day but quoted during this period, is worth noting as evidence of the generally relaxed attitude toward child rearing:

> "If a babe sucks his thumb
> 'Tis an ease to his gum:
> A comfort, a boon, a calmer of grief
> A friend in his need affording relief;
> A solace, a good, a soother of pain;
> A composer to sleep, a charm and a gain. . ."[8]

The swing of the pendulum away from love and affection was represented by those writers who were concerned that children were "getting away with too much and that it was time they were punished." Whereas in 1890 writers advised using rewards as a method of disciplining, by 1900 the interpretation of "discipline" involved punishment. Fourteen per cent of the articles questioned "the singular theory of education, that boys are to be left scrupulously alone, freed from any restraint or fear of punishment to grow as nature chooses,"[9] and restraints, ridicule, even pepper on the tongue for lying were suggested as disciplinary measures.[10]

Before moving on to the next period, perhaps a word of explanation is in order regarding child-training practices listed under Invoke Divine Aid in Table II. It should be noted here that 1890, 1900, and 1910 saw many more references of a spiritual nature than any of recent years. God had given parents their wee ones, God's help should be invoked in bringing up these wee ones, and

parents should provide a good *Christian* home in order to develop good moral character. References to God rarely appeared after 1910; indeed to the reader brought up in the secular culture of today, such references seem strangely out of place in magazines which are not published by religious groups.

By 1910, while, as Table I shows, interest in the same kinds of topics as had appeared in the two earlier periods persisted, there had been a striking shift in what was being advocated as good child-rearing practice. Mothers were still interested primarily in good character development, but the means to a good character was no longer through a shower of love. In Table II the reader can see that discipline (again interpreted as punishment) had been extolled as a means of producing good character in 14 per cent of the articles in 1900, whereas in 1910 this figure had changed to 34 per cent. Providing a Good Home Influence had dropped from 53 per cent in 1900 to 30 per cent ten years later. An even more dramatic shift in kind of advice is seen in the change to 77 per cent advocating a *strict* schedule in 1910 from 22 per cent in 1900.

Perhaps the following quotation, in contrast to the advice given on thumb-sucking in 1900, may symbolize the change. With regard to nail biting, one expert wrote, "Get some white cotton gloves and make her wear these all the time—even in school. They will not only serve as a reminder but also make her ashamed when people ask her about them." Mothers were admonished to insist upon obedience at all times, and if temper tantrums resulted, they should be ignored. Together with a more severe attitude toward the child went a new taboo on physical handling. Love, and particularly the physical manifestation of it, was discouraged in most of the articles on Infant Disciplines. It was believed that stimulation of any sort would lead to precocity in the older child and dullness in the man. Furthermore, baby's strength was needed for rapid growing, and picking the baby up deprived him of his strength. Still another reason for discouraging physical contact with baby was the belief that postnatal conditions for the infant should closely approximate prenatal conditions, and since the infant was not handled in the uterus, he should not be handled after birth.

So great had been the swing in a short twenty years that only a few daring writers raised voices in protest. One author summarized contemporary theories of child rearing, somewhat hesitantly attacked them, and then made a plea for the return of the old-fashioned mother who picked her child up when he cried, "Perhaps the greatest recent upheaval of nursery law is that which has been disciplining the young mother to hear her child's crying and make no response whatever. . . It is good for some children to be allowed the privilege of crying unmolested, but there are. . . some children who are definitely more or less seriously injured by this kind of neglect. . . Perhaps it might be better for many young mothers if they had never heard of such a thing. . ."[11]

It is difficult to find any clear evidence as to the reason for the dramatic shift in opinion in child-rearing practices in the course of twenty years. While child psychology as a scientific subject had had its beginning in the 1880's, the leaders of that movement had furnished no experimental evidence which would lead to a change from a sentimental, indulgent attitude toward children, to one

of regimentation and sternness. Apparently the writers of the 1900-1910 period, like their predecessors, were merely airing their own personal opinions. The form which their personal opinions took may have been motivated by current intellectual concerns. The turn of the century was characterized by a zeal for reform which left few aspects of American life untouched. One of the concerns had to do with the appalling rate of infant mortality prevalent at the time in this country. As part of the campaign for healthier babies, doctors were advocating a stricter feeding schedule for infants and advising mothers to let babies cry if they demanded food before the scheduled time. From the scheduling of feeding it may have been but a step to regimentation in other aspects of the baby's life. With the American people ripe for reform, it would not be hard for such a movement to gain momentum. This, however, is mere speculation. What is clear is that "experts" had completely reversed their stand since 1890, and that the new dogma was being advanced just as vigorously and positively as the previous one, and with just as little scientific backing for it.

A glance at the figures in Table I for the years 1920-1921 reveals a sharp change in the kinds of articles appearing in the magazines. While interest in Physical Development and Specific Behavior Problems continued high, only 3 per cent of the articles dealt with Character Development and the largest percentage of articles had to be listed under Miscellaneous. A careful analysis of the miscellaneous articles showed that many of these had to do with social legislation. Again we turn to the larger cultural scene for an explanation of this interest. Women were suffrage-minded; for the first time it was their privilege to be able to influence, through their votes, legislation of interest or of benefit to them. Militant writers were attempting to help them become better informed on social problems involving children, and so articles urging legislation with regard to child welfare, child labor, and child health appeared.

The articles on physical development were devoted mainly to nutritional problems. Many of these articles carried words of warning designed to make the parent aware of her child's difficulty, as, "Parents of older children are not awake to the urgent need of attention to their proper growth and nutrition. Many of these children are carrying the cumulative effects of years of underdevelopment and malnutrition."[12] Parents and teachers both were urged to keep height-weight charts for children and, "Every child over the top,"[13] was the slogan of the day. Malnourishment was also seen as being related to good character development, and several writers would have parents cure behavior problems by feeding children properly. Of the few articles dealing with character development, half of them dealt with the connection between a well-nourished body and good moral character. The following quote shows that malnutrition was also seen as a social evil. "Malnutrition is a foe of the community. No child is safe while any child suffers."[13] Undoubtedly the war, which had revealed large numbers of malnourished recruits, was partly responsible for this emphasis.

All of the articles dealing with Infant Disciplines advised rigid feeding schedules, early toilet training and letting baby cry it out, but for a different reason at this time. Whereas in 1910 children were to be left alone because

stimulation might lead to precocity or because that was the way Nature intended them to be raised, in 1920 the impact of Watsonian Behaviorism was beginning to be felt. J. B. Watson some years earlier had emphasized that the psychologist must study behavior, rather than the thoughts and dreams of man. Each act of behavior was caused by a particular stimulus which set up in the nervous system a connection leading to a particular response. Now scheduling was important in order that baby might be conditioned to feeding or sleeping or toiletting at a particular time. Parents were told that if baby were to be picked up just once when he cried, he would be "conditioned," that is, he would learn that the stimulus, crying, produced a particular response, being picked up, and a bond between the two would be set up in his nervous system. On the other hand, a properly trained baby would result if, "Everything done for him (were) so regular that one can tell time by what is going on in the nursery."[14]

One lone voice discussing the development and expression of individual personality was the first expression of popular Freudian theory to be found in the literature examined. "Of equal importance, during the years of plasticity in the life of a child is the avoidance of any act tending to produce in after years, what the psychoanalysts call infantile fixation. . . at this time command and exhortations are worse than no avail. . . every manifestation of objectivity on the part of a child should always be encouraged. The child should be encouraged to tell his fears. . . one supreme spiritual function of the parent is to unload unpleasant emotions from the soul of the child. If they are not allowed to find expression in some way, they will, in the child's later life as an adult, do considerable damage because of their continued accumulation. . ."[15]

The year 1930 was a low year with regard to the number of articles on child rearing with only forty-nine articles appearing in the three magazines studied. Interest in physical development reached a new high, with about one-half of the articles on child rearing being devoted to information on nutrition, sleeping habits, childhood diseases, and the like. The up-to-date mother was one who knew her calories and her vitamins, who fed her family scientifically, and who saw that her baby had fresh air (however cold), and sunshine. Interestingly enough, along with increased interest in scientific feeding in the twenties and thirties went more attention to feeding problems. There were more articles devoted to finicky eaters and slow eaters during these two decades than at any other time.

Interest in Character or Personality Development had revived, with 24 per cent of the articles in 1930 devoted to this topic as compared with only 3 per cent in 1920. Now for the first time, the emphasis in this area was on *personality* rather than *character* development. Emotional problems of adjustment rather than moral problems claimed the attention of the writers. Articles under this category as well as those under Infant Disciplines continued to show a rigid approach to child training, as Table II shows. The influence of J. B Watson on child training had made tremendous gains in the twenties and continued to grow in popularity in the thirties. The popularity of this school of child rearing can best be understood in the light of two important cultural

trends. One of these trends was the great increase in the prestige and importance of science during the twenties. The American public had been sold on science. New machines and gadgets in homes and factories testified to the efficiency of science. Psychology shared in this prestige; it, too, was scientific and infallible, and if psychologists said babies were spoiled by picking them up when they cried, then Baby was to be left to cry it out. The twenties had also ushered in the era of the flapper, with her intense scorn of Victorianism and everything it symbolized. Grandmother's ideas of raising children were old-fashioned and unscientific, and the extreme sentimentality toward children of a generation before was replaced by a cynicism which frowned upon mothering and cuddling and the rocking chair. The American mother of 1930 was ripe for bringing her baby up on a book written in accordance with the latest psychologic theory, particularly when that theory was the exact opposite of child training ideas of the decade she was repudiating.[5]

The twenties had also seen widespread acceptance of Freudian theory and many extreme applications of it to the training of children. Freudianism had generally been interpreted to mean that repression was bad for the child. The unfortunate results of bringing children up without limits had received considerable criticism in the late twenties, and perhaps part of the popularity of behaviorism in 1930 was due to a reaction to psychoanalytic theory.

But while the "feed-'em-on-schedule, let-'em-cry-it-out" school of thought with regard to child training undoubtedly continued to influence practice well into the thirties, there were a few harbingers in the 1930 periodicals, of the change that was to come. Late in 1930 Dr. Karl Menninger began a series of articles entitled "Mental Hygiene in the Home."[16] These articles dealt with the emotional adjustment of children and presented in case-study fashion general psychologic principles applicable to child rearing. The influence of the home and the importance of finding the cause of behavior were emphasized. Dr. Josephine Kenyon, during that same year, wrote more specifically concerning certain child training practices, "Then (ten years ago) we felt that the digestion of a baby should be expected to fit our rather set theories of infant feeding. Now. . . we are more apt to conform to the needs of the individual baby."[17]

By 1940, the percentage of articles dealing with personality development once more rivaled the percentage dealing with physical development. Twenty-three per cent of articles dealt with the former while 22 per cent dealt with the latter, as Table I shows. Furthermore, the data in Table II reveal that child-training procedures had changed considerably. While 33 per cent of the articles in Infant Disciplines followed a modified behavioristic style, 66 per cent were advocating self-regulatory, permissive procedures. The swing from the "be-tough-with-them, feed-on-schedule, let-them-cry-it-out" doctrine of the twenties and thirties was almost complete, with many articles emphasizing the connection between Infant Disciplines and later personality development. "It is reasonable to feed a baby when he's hungry," wrote one authority, "It is unreasonable to make him wait. . . Studies of so-called spoiled children and their homes have shown that they were denied adequate 'mothering'."[18]

Developmental aspects of behavior also received attention, with 10 per cent of the articles describing what children are like at different age levels. Temper tantrums or thumb-sucking or lying or bad manners were seen as passing phases in a child's life and could best be treated by ignoring. They were no longer considered to be problems, but were, rather, normal behavior for certain age groups.

Attention should also be called to the large increase in the percentage of articles emphasizing that behavior is a caused phenomenon. Forty-eight per cent of the writers pointed out that in guiding personality development one should look for the cause before prescribing treatment. Case-study material was presented to show how certain personality patterns had developed, and implications were drawn for sound personality development.

Today in lectures and in texts the modern mother continues to be exposed to advice in the "mothering, delayed-toilet-training, wean-'em-late" school of thought. She is admonished to nurse her baby if possible, to feed baby on a self-demand schedule, to give baby plenty of mothering and cuddling. She is told that in these ways she supplies an atmosphere of emotional security important for the development of wholesome personality. But, more prominent in the magazines studied is an emphasis which first appeared in 1930—a mental hygiene approach to rearing children. It is an approach which emphasizes the importance of good emotional health and tries to point out ways in which this can be developed. The child's need for love and affection if he is to be a secure individual is stressed, as is the necessity for understanding the child and accepting him for what he is. Of the articles dealing with personality development, 84 per cent were pointed in this direction.

IMPLICATIONS OF THE STUDY

At first glance it might appear that the circle has been closed; that we have ended up in 1949 at exactly the same point with regard to child-rearing practices at which we began in 1890. However, a careful examination of the literature will show that this is not true. Observers in 1890 witnessed a sentimental, highly emotionalized concept of the mother, with much emphasis upon how the child acquires good character by imitating the mother. The present-day writer emphasizes the importance of the mother, but not in a highly sentimental fashion. A mother is important because in "mothering" or cuddling her baby she imparts to even a very young infant a feeling of well-being or security which is most important for his personality adjustment. Indeed, it is very likely that the 1949 expert might accuse the mother of 1890 of "smothering" her baby with a sickeningly sweet kind of love.

But just as the effusive, sentimental approach of the nineties and the rigidly regimented approach of later decades have seen their day and disappeared, so the handwriting is on the wall as far as certain *faddish* aspects of present practice are concerned. 1890, with its romantic and sentimental descriptions of the mother-child relationship might seem funny to 1920. Similarly, the words of wisdom of 1920 and 1930 are preposterous to the mother of 1949, "If you can, start training your infant to have a bowel movement in the chamber each morn-

ing at the age of one month. . . Fix upon a definite time, . . . place the chamber on your lap. . . and hold the infant over it. . . Insert about two inches into the rectum, a tapered soap stick, keep it there from 3 to 5 minutes. . . The movement will usually occur under this stimulus. If you keep this up with regularity, a daily bowel movement will probably result."[19] Just as ridiculous to the 1960 parent, however, may seem the 1949 counsel, "When a baby cries on, trying in vain to tell his wants, he may even come to feel, 'The world is against me,' "[20] and some of the current advice on the relationship between too early toilet training and the development of an overly meticulous personality with a compulsion for neatness and punctuality.

Furthermore, it would seem that the permissive theory has in some cases been interpreted in an extreme fashion. Inexperienced mothers, just home from the hospital, have difficulty in deciding when Baby's cry indicates hunger, and many an infant is being fed too often for his own comfort by an anxious mother who fears to ruin his personality by letting him go hungry. Dr. Spock has recently discussed another kind of problem in connection with the permissive approach, and that is the problem of a "gentle, uncertain, long-suffering type of mother" who has been convinced that baby should be comforted when he cries. Her basic uncertainty makes it difficult for her to set sensible limits, so that the baby develops a determined kind of personality and successfully bullies his mother into giving him an inordinate amount of attention.

But criticism of the permissive theory of infant care does not mean that the old rigid approach was better. Criticism in no way implies that we should return to the heartless methods of the thirties. It simply means that we apply the new theory with caution and with due regard for individual differences in personalities of babies and mothers. The "martyr" type mother whose personality is such that she tends toward overprotection may need to be helped to set reasonable limits to her baby's demands upon her, just as the "uncertain" mother whom Dr. Spock describes.

Nor does this criticism mean that there has been no advancement in this field since 1890. The evidence from child development laboratories and child guidance clinics would seem to indicate that there are certain general truths which have evidenced themselves in so many ways and over so long a period of time that they may be accepted. We know, for example, that different aspects of behavior are interrelated, and that poor physical health may be caused by emotional difficulties. We know that behavior is caused, and that it has its roots in early childhood experiences. We know that human beings have certain emotional needs, just as they do physical needs, and that these needs must be satisfied if an individual is to grow up healthy in mind and body. But the specifics of these general truths we do not know. It would seem evident that children need to feel loved to thrive, but how the feeling of being loved is communicated to a young baby is a matter of speculation. The feeling of affection may be keenly sensed by the child whose mother may schedule his feeding or his toilet training, but whose warm-hearted acceptance of him may be communicated in very subtle ways. In the same way, a feeling of rejection may be

felt by the child whose mother follows the 1949 book and feeds on a self-demand schedule, but who "cuddles" only from a sense of duty and not because she has any zest for the job. We cannot order or prescribe love, and when we make a dogma out of it we may only add to the guilt feelings of those parents whose own emotional difficulties keep them from wholehearted acceptance of their children. What we can do, what certainly needs to be done, is to help parents develop insight into their own personalities in the hope that they can more intelligently approach problems of child rearing. No trend in this direction has been noted in the literature examined.

SUMMARY

This study has been a survey of, approximately, the past sixty years in child training. Three different schools of thought have prevailed with regard to how children should be raised. The 1890's and 1900's saw a highly sentimental approach to child rearing; 1910 through the 1930's witnessed a rigid, disciplinary approach; the 1940's have emphasized self-regulation and understanding of the child. These sixty years have also seen a swing from emphasis on character development to emphasis on personality development. Each period studied has had its share of fads with regard to child training. It would appear that the present fad may be an extreme emphasis upon the relationship between specific infant disciplines and later personality development. Parents and others in the field of child guidance are warned that, while certain general truths have been discovered, we still do not know the specifics with regard to child training practices. Parents and others are also warned to beware of "mother's instinct" or "common sense," for this has had radically different meanings for practice during the past sixty years.

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Comments on Current Literature

THE USE OF BLOOD FROM FEMALE DONORS IN THE TREATMENT OF ERYTHROBLASTOSIS FETALIS

STATISTICAL studies and laboratory investigations which are in progress at the Blood Grouping Laboratory of Boston are drawing attention to the beneficial effect of blood from female donors for exchange transfusion in the treatment of erythroblastosis fetalis. In a recent issue of the *New England Journal of Medicine*[1] (Nov. 24, 1949), Allen, Diamond, and Watrous report their experiences in the treatment of 205 infants with erythroblastosis fetalis who received replacement transfusion of at least 150 c.c. of blood by way of the umbilical vein. Of 137 infants receiving blood from male donors only, 27 died, a mortality of 19.7 per cent; of 42 babies receiving blood from female donors only, none died.

While the over-all results in this large group of infants with erythroblastosis fetalis indicate quite favorable response to blood from female donors, the authors have been careful to weigh many possible factors which may be influencing the significance of these statistics. In a completely objective manner they subject their findings to clinical, as well as statistical, analysis. It was noted that by chance, blood from female donors had been chosen for transfusion of male babies, a group which on the basis of previous experience, might be expected to have a somewhat less favorable prognosis. On the other hand, blood from male donors had been used in a significant number of instances for the transfusion of the "sicker" babies. This is in accord with the general tendency to select blood with higher packed red-cell volume, almost invariably from male donors, when the infant was very ill. Nevertheless, the beneficial effect of blood from female donors was very striking in a group of babies whose red-cell counts were low.

In a comprehensive summary, reproduced in Table 8, the authors present in tabular form the results of a statistical analysis* of clinical factors which may have bearing on the general conclusions.

The occurrence of kernicterus in infants with erythroblastosis fetalis is a serious problem and merits special attention. The authors point out that on the basis of previous studies the most evident sex difference among the babies is the marked relative infrequency of kernicterus in females. It was hoped that the incidence of kernicterus might be lower when blood from female donors was used for transfusion. However, close attention to this point in analyzing the figures revealed an incidence of 7.2 per cent of kernicterus in the group of babies receiving blood from female donors as compared with 8 per cent in the group receiving blood from male donors.

It is the opinion of these investigators that whatever the beneficial effect of blood from female donors in the treatment of erythroblastosis fetalis, the beneficial component of the blood must be shared by virtually all young women. It is probably present in dilute form since relatively large quantities

*Table 8. In statistical evaluation X^2 in each case was determined by the use of 2×2 contingency tables.

TABLE 8. CONSOLIDATED STATISTICAL DATA

CLINICAL DATUM	CLASSIFICATION	SURVIVAL (%)	MALE DONORS	FEMALE DONORS	PERCENTAGE OF FEMALE DONORS	SURVIVAL ACCORDING TO SEX OF DONOR		
						MALE DONOR (%)	FEMALE DONOR (%)	X^2
All babies receiving blood from donor or donors of one sex (179 cases)		85.0	137	42	23.4	80.3	100	9.73
Severity of disease at birth	None or mild	95.8	65	28	30.1	93.9	100	0.61
	Moderate or severe	73.3	72	14	16.3	68.0	100	4.58
Baby's red cell count	Over 3,000,000	95.1	55	26	32.1	92.8	100	0.63
	3,000,000 or less	73.3	59	12	16.9	67.8	100	3.75
Mother's titer	Less than 1:64	84.7	66	25	27.5	78.8	100	4.74
	1:64 or higher	81.9	54	12	18.2	77.8	100	1.93
Ratio of mother's titer to baby's titer	1-8	87.0	64	20	23.8	83.0	100	2.60
	16 or higher	79.5	56	17	23.3	73.3	100	4.20
Length of gestation	38 wk. or longer	89.2	97	23	19.2	86.7	100	2.21
	Less than 38 wk.	75.0	38	18	32.2	63.2	100	6.98
Amount of blood given	400-500 c.c.	91.3	70	23	24.7	88.5	100	1.59
	All other	78.0	67	19	22.1	71.8	100	5.35
Age when started	Over 3 hr.	86.5	56	18	24.3	82.2	100	2.34
	3 hr. or less	84.2	77	24	23.7	79.3	100	4.47
Age of blood	0-9 days	86.1	87	28	24.3	81.7	100	4.54
	Over 9 days	84.7	41	11	21.1	80.5	100	1.25
Chronologic period	Since 3/11/48	87.5	69	19	21.6	84.1	100	2.15
	Before 3/11/48	82.5	68	23	25.3	76.5	100	5.04

of blood seem to be needed in order to assure good results. Whether the concentration of the beneficial component (or components) depends on age, parity of the donor, menstrual phase at the time when the blood was taken, or on some other factors, must await further evaluation. Fractionation studies are in progress with a view to ascertaining which blood elements are associated with the beneficial component.

While extensive investigations are needed in this field before general conclusions can be drawn, especially a need for similar analyses of statistical results from the records of other well-run clinics, "it appears that, for the present, exchange transfusion, using blood from a female donor, is the treatment of choice in babies with erythroblastosis fetalis."

RUSSELL J. BLATTNER.

REFERENCE

1. Allen, Fred H., Diamond, Louis K., and Watrous, Joseph B.: Erythroblastosis Fetalis: V. The Value of Blood From Female Donors for Exchange Transfusion, New England J. Med. **241**: 799, 1949.

News and Notes

Pediatric Calendar for 1950

American Board of Pediatrics:

Oral examinations:

Richmond, Va., Feb. 10 to 12.

Philadelphia, Pa., March 31, April 1 and 2.

San Francisco, Calif., June 23 to 25.

American Academy of Pediatrics:

Area meeting: Philadelphia, Pa., March 31, April 1 and 2.

Annual meeting: Chicago, Ill., mid-October.

American Pediatric Society:

Annual meeting: French Lick, Ind., May 9 and 10.

Society for Pediatric Research:

Annual meeting: French Lick, Ind., May 8 and 9.

Section on Pediatrics, American Medical Association:

Annual meeting: San Francisco, Calif., June 28 to 30.

Sixth International Congress on Pediatrics:

Zurich, Switzerland, July 24 to 28.

The **Nutrition Foundation** has made a grant of $3,000 annually for three years to Dr. P. C. Jeans of the University of Iowa for the study of the effects on the infant of prenatal vitamin K deficiency in the mother.

Dr. J. Lawrence Slobody has been appointed professor of pediatrics and director of the department at New York Medical College. Dr. Slobody succeeds Dr. Reuel Benson who will become professor of graduate pediatrics.

Dr. James F. Bosma, formerly of the University of Minnesota, has been appointed professor of pediatrics at the University of Utah Medical School.

Dr. Katharine Baird of Milwaukee, Wis., died of poliomyelitis early in November.

A grant of $10,000 from the **Uhrig Foundation** has been made to Marquette University School of Medicine to employ a full-time instructor in pediatrics who will carry on teaching activities at the Milwaukee Children's Hospital.

According to estimates prepared by the **Office of Vital Statistics**, the birth rate for the first nine months of 1949 continued at a high level, and only 4 per cent below the peak year of 1947. There were 2,669,000 registered births during the nine months, which is a rate of 24.1 per 1,000 population on an annual basis.

Final figures for 1948 show a total of 3,702,000 registered and unregistered births as contrasted with 2,558,000 in 1940. In both these years the armed forces formed a very small part of the total population. The percentage increase between the two years is 35.2. An increase was found in every state and was greatest in Colorado and Rhode Island. The birth rate for 1948 was 24.2. New Mexico, with 35.9, had as usual the highest rate, and Massachusetts, with 20.0, was lowest.

A continuation course in pediatrics for general physicians will be presented at the **Center for Continuation Study of the University of Minnesota** on January 26 to 28, 1950. The course will be divided into three major divisions. A short period will be devoted to the importance of hereditary and genetic factors in understanding pediatric problems. A second portion of the course will emphasize common dermatological problems seen in infants and children. Common infectious diseases will be considered in the third portion of the course. Dr. Franklin Top, of the Herman Kiefer Hospital, Detroit, Mich., will be the visiting faculty member for the course.

The National Foundation for Infantile Paralysis announces that it is offering postgraduate research fellowships for from one to three years in the fields of pediatrics, virology, epidemiology, orthopedic surgery, and neurology. Candidates must have two years' residency training in the specialty. Additional information and applications may be obtained from Professional Education Division, The National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y.

The Society for Pediatric Research announces the appointment of seven additional Mead Johnson Fellows for the academic year 1949-50. The following Fellows have been appointed:

Dr. C. T. Lee from China
Dr. Solomon A. Kaplan from South Africa
Dr. Carlos A. Bauza from Uruguay
Dr. Isabelle Valadian from Lebanon
Dr. Ramon Sanz Munoz from Mexico
Dr. Dacio Pinheiro from Brazil
Dr. Jorge Arguedas Soto from Costa Rica

Book Reviews

Dental Caries. Clinical and Experimental Investigations. T. Ockerse, D.M.D., D.D.S., Pretoria, 1949, issued by the Department of Health of the Union of South Africa, 80 pages.

This is an excellent study of dental caries in South Africa. Nearly 80,000 European school children were examined in different parts of the country and 85 per cent were found to have caries. The percentage was higher among urban children than rural. Endemic dental fluorosis is widespread in South Africa and 805 endemic areas were mapped. Of 3,067 children with mottled enamel only 28 per cent had caries and of 9,806 children in these areas without mottling the incidence was 69 per cent. Definite evidence was found that fluorine in the drinking water is associated with a lowered caries incidence rate. The diet appears to be the most important contributing factor. High carbohydrate-low protein diets are associated with a high rate and vice versa. The monograph is attractively printed and contains a group of ten maps showing the geology, vegetation, fluorosis areas, etc., of South Africa. The study confirms current thought as regards caries in the United States. In two early chapters the author gives a valuable résumé of the factors influencing dental development, and of the world literature on factors which have been considered local contributory causes such as the saliva, acid-base character of foods, and oral bacteria.

Abraham Levinson Anniversary Volume. Studies in Pediatrics and Medical History. New York, 1949, Froben Press, Inc., 365 pages. Price $6.00.

This is a volume edited by Dr. Solomon Kagan in honor of the sixtieth birthday of Dr. Levinson. Forty-seven of his pediatric friends and colleagues interested in medical history have contributed articles to the volume. The articles are grouped according to Dr. Levinson's special interests: Pediatric Neurology and Psychiatry (6), Blood and Cerebrospinal Fluid (7), General Pediatrics (13), and Medical History (7). To this is added a bibliography of over 200 contributions to medicine by Dr. Levinson. Most of the contributions in the volume are by his Chicago associates. It is a very fine honor to a prodigious worker with interests in many fields of medicine.

Epilepsy and Convulsive Disorders in Children. Edward M. Bridge, New York, 1949, McGraw-Hill Book Company, Inc., 670 pages. Price $8.50.

This new book is an invaluable contribution to medical literature. Every physician, nurse, or social worker who has occasion to attend or to work with children suffering from epilepsy or epilepsy-simulating states will profit immeasurably by consulting it. Laymen who seek knowledge and correct orientation for themselves or others regarding the subject will find it extremely helpful and exceptionally interesting.

Being based upon the results of numerous scientific studies carried out during recent years by the author and other workers in the field, as well as upon his extensive practical experience in a large clinic on convulsive disorders, the treatise is authoritative in every respect. Yet, it is concise and is written in an exceptionally admirable style. One of the most distinctive features of the book is the profusion of well-chosen, meaningful illustrations pertaining to the etiological factors, the diagnostic procedures, and the prophylactic as well as therapeutic resources now available.

The appendix contains many record forms and tables of useful data pertaining to special diets, lists of occupations suitable for epileptic patients, drug prescriptions, and so forth. Nothing of importance appears to have escaped the author's attention. The alphabetical list of references to the literature on the subject is fairly extensive, filling twenty pages.

McQUARRIE.

1949 Year Book of Pediatrics. Edited by Henry G. Poncher, M.D., and Julius B. Richmond, M.D., Chicago, 1949, The Year Book Publishers, Inc., 560 pages. Price $4.50.

The most important pediatric literature that appeared during the last half of 1948 and the first half of 1949 is abstracted and reviewed. The editorial comment which was started in the 1948 edition has been extended and adds much to the value of the abstracts. There is a brief review of the main developments and trends in pediatrics during the period covered, and the editor indicates the trends in research. It is well written, the material selected is excellent, and this volume sets a high standard. Dr. Julius Richmond, Associate Professor of Pediatrics at the College of Medicine of the University of Illinois, has become associated with Dr. Poncher in editing the Year Book.

Medicine Throughout Antiquity. Benjamin L. Gordon, M.D., Philadelphia, 1949, F. A. Davis Company, 818 pages. Price $6.00.

Physicians will find in this book a readable account of the very beginnings of medicine. The field covered is from the scant evidences found in prehistoric man through Galen (131-200 A.D.). The author considers three periods of the medicine of antiquity: the first, from the birth of man to the time when history was recorded; the second, ending with the rise of the philosophical school of Iona about 600 B.C.; and the third, ending with the decline and fall of Rome about 467 A.D. Chapters are devoted to medicine in ancient Babylonia, Egypt, Persia, China, and Japan. Of particular interest is the story of medicine among the prehistoric Amerinds. The Greco-Roman period falls in with the more usual handling of ancient medicine. The book does not have to be read through steadily but can be recommended for "browsing" when the time and mood fall together.

Editor's Column

THE PROFESSION AND THE "SERVICE STATE"

IN A recent address* a distinguished lawyer and educator, Roscoe Pound, a former dean of the Harvard Law School, discusses the development of the professions and their problems in the society of today. A profession is defined as "an organized calling in which men pursue a learned art and are united in the pursuit of it as a public service." He stresses the fundamental differences between medical or bar associations and trade organizations—the former existing primarily for the purposes of advancing the professions, while the trade organization exists for money-making activities. He feels that the professional traditions of the duty of the physician to his patient and the lawyer to his client cannot be replaced with benefit to the public by a political tradition of office holders holding allegiance to political parties.

Although in the early days of America political thought was dominated by fear of governmental oppression of the individual, throughout the world during the present century there has been a steady rise of the "service state" which performs all manner of services for the people instead of leaving them free as possible to serve themselves. The essayist feels that when every form of public service becomes potentially a state function, the difference between a public service performed by a profession and a public function performed by a bureau becomes crucial.

Dean Pound sees four sources of menace to the professional ideal in the society of today: first, the exigencies of individual economic existence; second, the multiplication of detail in every branch of learning which necessitates cooperation of practitioners in which individual responsibility may become merged; third, when this stage is reached the difficulty of resisting the pressure of business methods; and, finally, when this stage is given impetus by the advent of the service state with the tendency to commit all things to bureaus of politically organized society.

While the essayist states, "I am not here to speak against the service state," he also says, "the idea of a profession is incompatible with performance of its functions or the exercise of its art, by or under the immediate supervision of a government bureau. . . . The service state began by performing a few major services. In time it had undertaken more and more. Now it seems jealous of public service performed by anyone else." Dean Pound makes it clear that he is not preaching against the service state in itself, as the society of today demands services of the state beyond simply maintaining order and repairing injuries. What he feels must be resisted is not the state performance of many public services, but the idea that all services must and can only be performed by the government. "The service state is a political step forward. But we must not

*Pound, Roscoe: The Professions in the Society of Today, New England J. Med. 241: 351, 1949.

let it turn back upon itself and lead to absolutism. There is no surer route to absolutism than an unchecked omnicompetent bureaucracy."

We have quoted from these remarks of a distinguished leader of a sister profession as they express so well the thought and fears of many of us who recognize, as Dean Pound has done, that the service state is a political step forward, and furthermore that we must face the fact that it is with us. Nevertheless, we fear greatly the danger to the professional ideal under bureaucracy, which seemingly is a necessary part of the service state. The real problem that must be faced is how professional ideals can be maintained in the changing social structure of today. It cannot be met by simple stubborn opposition to change and unconstructive criticism.

* * * * *

There are some proponents of "socialized medicine" (whatever this term may mean) who take the attitude that there is no danger to the professional ideal in bureaucratic controlled medicine—that this so-called danger is a straw man erected by the diehard reactionaries. To them we would recommend the reading of an unusual article which appeared some months ago by Dr. Leo Alexander, a Boston psychiatrist, who was consultant to the Secretary of War on duty with the office of the Chief of Counsel for War Crimes in Germany, 1946 to 1947.* Although socialized medicine is not mentioned, it is in some respects the best argument against allowing the control of medical practice to fall into the hands of the bureaucracy of the "service state," to use Dean Pound's term, that we have seen. Dr. Alexander describes the degradation of medicine in Germany under the Nazi rule. From euthanasia for hopelessly ill, chronic, mental patients, it was a gradual but direct step to the medical extermination of races, and finally to the murder by medical means of those who were political offenders. This was accompanied by revolting forms of human vivisection in the name of medical research. Dr. Alexander traces the motivation of the men involved as one of clearing themselves of the charge of disloyalty to the ruling political party. Professional ideals became secondary. While this is an extreme example of the effect of politically controlled medicine on professional ideals, and it is inconceivable that such a development would ever take place in this country, those who so blandly state, "There is no danger to the professional ideal in bureaucratic controlled medicine," should read Dr. Alexander's article. We warn you it is not pleasant reading, but it has made a deep impression on the thought of the editor and others with whom he has discussed the article.

B. S. V.

ROSEOLA INFANTUM (EXANTHEM SUBITUM)

LITTLE has been added to our knowledge of roseola infantum, or exanthem subitum as many prefer to call it, since Zahorsky first described it as a clinical entity in 1910, and Veeder and Hempelmann in 1921 pointed out that leucopenia with a relative lymphocytosis is one of its chief diagnostic features. Berenberg, Wright, and Janeway in the Aug. 18, 1949, issue of *The New England*

*Alexander, Leo: Medical Science Under Dictatorship, New England J. Med. 241: 39, 1949.

Journal of Medicine have published an excellent summary of present-day thinking about this most intriguing disorder, and advance hypotheses to explain some of its peculiarities.

Most pediatricians in private practice are familiar with the disease and have become quite adept at predicting the sudden appearance of a measles-like rash following the asymptomatic febrile episode of three to five days. However, general physicians and the public are not so well informed, and frequently it is passed off as "measles" or a drug rash.

Thus far all attempts to identify an etiologic agent have been unsuccessful. While the characteristics of the disease suggest a virus as the most probable cause, yet the methods usually employed for the detection of viruses have yielded only negative results. Were it not for the fact that several institutional outbreaks have been observed, one might have serious doubts about an infectious origin. Physicians who have had abundant experience with cases of roseola both in the home and in the hospital have repeatedly reported the infrequency with which second cases are seen.

But now comes an amazing report from the British Isles, published in the March issue of *Archives of Diseases of Children*, by James and Freier, of an outbreak in a maternity hospital in which nurses, mothers, and fathers, as well as young infants were affected. Nineteen of sixty-five babies on the floor developed the disease, the age of onset varying from 8 to 12 days with an average age of 11 days. Berenberg, Wright, and Janeway, referred to above, affirm the usually accepted distribution curve of 95 per cent of all cases occurring between the ages of 6 months and 3 years. They mention Zahorsky's 2-week-old patient and the 31-year-old woman seen by Cutts. Both Cushing and Barenberg (L. H.) have reported epidemics in foundling institutions and have established the usual incubation period as being from ten to fifteen days. But nowhere in the literature is there to be found any such remarkable report as this one from London. Since the onset of the disease in the infants was confined to such a short period, it is obvious that the method of spread was in all probability not from infant to infant. Whether or not it was thought exposure to an adult accounted for the cases in the infants is not discussed. Altogether five nurses and three mothers on the affected floor developed roseola. Six mothers and four fathers came down with it at home. In the mothers the onset was within fourteen days of the onset of roseola in their babies.

Berenberg, Wright, and Janeway advance the hypothesis that "widespread dissemination of the infective agent, perhaps by numerous adult carriers, universal susceptibility after disappearance of the antibodies received from the mother, and the existence of atypical modified forms of the disease" may account for the infrequent appearance of roseola before 6 months of age and after 3 years of age. If outbreaks like the one in the maternity hospital in London continue to be reported, this hypothesis will need modification.

Roseola infantum is an intriguing disease indeed! Someday someone will really have to get serious about challenging this young upstart, and find out what makes it behave as it does.

L. F. H.

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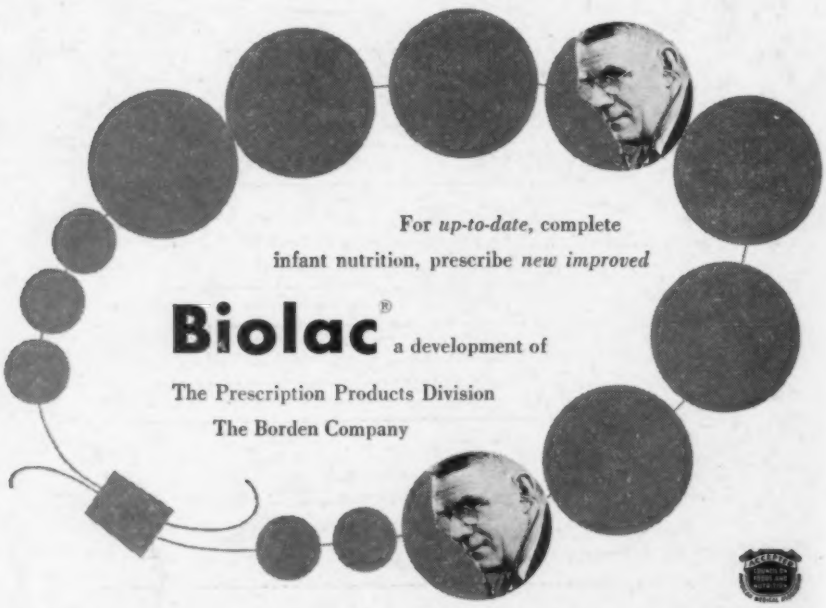

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